Epigenetic regulation in epilepsy: a novel diagnostic and therapeutic strategy for epilepsy

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Abstract

Epilepsy is a common neurological disorder in which excessive and abnormal neuronal discharges can be observed and is characterized by recurrent seizures. The epileptogenesis is usually involved in neuropathological processes such as ion channel dysfunction, neuronal injury, inflammatory response, synaptic plasticity, glial cell proliferation and mossin fibrosis, currently the pathogenesis of epilepsy is not yet completely understood. A growing body of studies have shown that epigenetic regulation, such as histone modifications, DNA methylation, noncoding RNAs (ncRNAs), and restrictive element-1 silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) are also involved in epilepsy. However, the functional roles of epigenetics in pathogenesis and treatment of epilepsy are still to be explored. Therefore, in this review, we will summarize latest advances concerning the mechanisms of epigenetic regulation in epilepsy, which provide novel insight into therapy and biomarkers for epilepsy.

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Highlights

1. In epilepsy, the epigenetic regulation is involved in epileptogenesis. We summarize the roles of histone modifications, DNA methylation, ncRNAs and REST/NRSF in epilepsy.

2. MicroRNAs may be the biomarkers for the diagnosis of epilepsy and is involved in treatment of epilepsy. LncRNAs may regulate epilepsy by targeting microRNA. As one of the regulatory mechanisms of microRNAs, m6A modification may be involved in the pathogenesis of epilepsy.

3. The mechanisms of epigenetic regulation in epilepsy may provide new strategies for the treatment of epilepsy.

Abstract

Epilepsy is a common neurological disorder in which excessive and abnormal neuronal discharges can be observed and is characterized by recurrent seizures. The epileptogenesis is usually involved in neuropathological processes such as ion channel dysfunction, neuronal injury, inflammatory response, synaptic plasticity, glial cell proliferation and mossin fibrosis, currently the pathogenesis of epilepsy is not yet completely understood. A growing body of studies have shown that epigenetic regulation, such as histone modifications, DNA methylation, noncoding RNAs (ncRNAs), and restrictive element-1 silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) are also involved in epilepsy. However, the functional roles of epigenetics in pathogenesis and treatment of epilepsy are still to be explored. Therefore, in this review, we will summarize latest advances concerning the mechanisms of epigenetic regulation in epilepsy, which provide novel insight into therapy and biomarkers for epilepsy.

Key words: epilepsy; DNA methylation; histone modification; noncoding RNA; N6-methyladenosine; restrictive element-1 silencing transcription factor/neuron-restrictive silencing factor;

1.Introduction

Epilepsy is a common neurological disorder in which excessive and abnormal neuronal discharges can be observed and is characterized by recurrent seizures(Chen et al., 2020). At present, antiepileptic drugs (AEDs) are still the major methods of treatment for epilepsy in clinic and about 1/3rd of patients with epilepsy are drug-resistant (DRE)(Moshé et al., 2015). The epileptogenesis is usually involved in neuropathological processes such as ion channel dysfunction, neuronal injury, inflammatory response, synaptic plasticity, glial cell proliferation and mossin fibrosis, whereby affecting neuronal function in the brain(Gan et al., 2015). Owing to the neuropathological process of epilepsy is complex and changeable, the pathogenesis of epilepsy is not completely clear, which brings difficulties to the prevention and treatment of epilepsy. In addition, an increasing number of epileptic patients with potential genetic causes fully proves that the regulation of genes may play a pathophysiological role in the epileptogenesis or progression of epilepsy.

In gene regulation, epigenetics mainly regulates gene expression through DNA methylation, histone modification and RNA methylation, so as to change the genetic information of organisms, but does not change the sequence of DNA nucleotides(Huang et al., 2021). At present, epigenetic mechanisms have been proved to be necessary to maintain neuronal function in the human brain(Hauser et al., 2018). A growing number of studies have shown that epigenetic regulation including histone modification, DNA methylation, ncRNAs and REST/NRSF, is also involved in epilepsy(Henshall and Kobow, 2015; Citraro et al., 2017; Butler-Ryan and Wood, 2021). In cultured hippocampal neurons of rats, it has been found that the cellular memory of epileptogenesis may be related to epigenetic regulation of epileptic target genes(Kiese et al., 2017). Importantly, epigenetic regulation can influence susceptibility and severity of SE, and in turn SE can also drive the changes of epigenetic markers that influence the expression of epileptogenesis-associated genes(Henshall, 2018). In the CNS, DNA methylation has been demonstrated to be involved in the expression of nerve cell-specific genes and is significantly altered in the animal models of epilepsy and human epileptic tissues(Zhu et al., 2012; Dębski et al., 2016). Meanwhile, improved cognitive function and hyperexcitability phenotypes after status epilepticus (SE) is also associated with altered DNA methylation(Henshall, 2018). In addition, in animal models of epilepsy and epileptic patients, altered histone acetylation have been thought to be involved in epileptogenesis and prolonged seizures also modify chromatin compaction by histone acetylation (Citraro et al., 2017; Henshall, 2018). Different brain-specific microRNAs have been observed to be abnormally expressed in animal models of epilepsy and epileptic patients, particularly in temporal lobe epilepsy (TLE)(Cattani et al., 2016). In addition, ncRNAs including microRNAs and lncRNAs have been studied in epileptogenesis and treatment of epilepsy and may play an antiepileptic role as a new therapeutic strategy since they have highly selective targeting(Xiao et al., 2018). MicroRNAs, as potential molecular biomarkers, can affect SE by targeting epilepsy-related gene networks through post-transcriptional mechanisms. Meanwhile, lncRNAs can also influence expression of some genes which are involved in electrophysiological functions of neurons by targeting microRNAs in epilepsy(Henshall, 2018). Thus, discovering new therapeutic targets related to epigenetics and exploring the correlation between epigenetics and epileptogenesis are crucial for the prevention and treatment of epilepsy. Here, we discussed the role of epigenetic mechanisms

in the occurrence and treatment of epilepsy.

2. Epigenetic modification inepilepsy

2.1DNA methylation

DNA methylation, as an epigenetic modification, has been shown to be involved in a variety of CNS disorders, including epilepsy(Portales-Casamar et al., 2016). DNA methylation refers to the formation of 5-methylcytosine (5mC) from cytosine under the catalytic action of DNA methyltransferase, which occurs mainly in cytosine-guanine dinucleotides (CpGs). In this process, DNA methyltransferases mainly include DNMT1, DNMT3a and DNMT3b(**Figure1**)(Heikkinen et al., 2022). In the genome of normal cells, most CpG sequences are methylated and the hypomethylated regions of DNA function are considered as elements to regulate gene expression, such as promoters and enhancers(Nishiyama and Nakanishi, 2021). Meanwhile, DNA methylation can also promote the binding of various transcription factors(Nishiyama and Nakanishi, 2021). Currently, two major regulatory mechanisms of DNA methylation in modifying gene activity have been proposed. On the one hand, DNA methylation can directly block the binding of transcription factors, resulting in gene silencing. On the other hand, DNA methylation can attract methyl-binding proteins, such as MBD1, MBD2, MBD3, MBD4 and MeCP2, which recognize methylated cytosine, thereby indirectly leading to the changes of gene expression(Heikkinen et al., 2022; Xie et al., 2022). In addition, the methyl groups required for DNA methylation depend mainly on the transmethylation of S-adenosine methionine (SAM) in the methionine cycle of organisms, resulting in the formation of S-adenosine homocysteine (SAH). Then, SAH is cleaved into adenosine and homocysteine. Adenosine kinase (ADK) is a cytoplasmic enzyme that catalyzes the conversion of adenosine to AMP. ADK activation represents the main pathway of adenosine clearance, which can increase the DNA methylation status of epigenome through the transmethylation pathway, whereas experimental or therapeutic adenosine augmentation prevents the reactions of DNA methylation(Williams-Karnesky et al., 2013). In epilepsy, ADK also regulates intracellular adenosine to modulate epileptogenesis by the epigenetic mechanism(Williams-Karnesky et al., 2013; Xu et al., 2017). In addition, the ketogenic diet (KD), as an important treatment for epilepsy, can enhance the production of adenosine which is a metabolic feedback inhibitors of DNA methylation(Lusardi et al., 2015; Longo et al., 2019). Relevant studies have shown that DNA methylation contributes to neuron cell-specific gene expression, which is significantly changed in the animal models of epilepsy and epileptic patients(Zhu et al., 2012; Dębski et al., 2016). In a word, nutrient metabolism and DNA methyltransferases may serve as a potentially modifiable upstream mechanism regulating DNA methylation in epileptogenesis.

In the KA-induced and pilocarpine-induced SE models, the similar patterns of DNA hypermethylation have been demonstrated in the epileptic hippocampal neurons (Murugan and Boison, 2020). Meanwhile, in the three models of chronic epilepsy (pilocarpine injection, focal amygdala stimulation and post-TBI), genome-wide changes in global DNA methylation were also investigated (Dębski et al., 2016). This study has concluded that changes in genomic DNA methylation provide the general pathological mechanism of epileptogenesis(Dębski et al., 2016). It have been reported that upregulated DNMT activity and associated changes of DNA methylation in patients with TLE, including focal cortical dysplasia (FCD)(Dixit et al., 2018). Moreover, FCD subtypes including FCDIa, FCDIIa and FCDIIb may also be distinguished by DNA methylation profiles, which suggesting that DNA methylation may serve as a biomarker for FCD(Kobow et al., 2019). Recently, a study about human epilepsy has shown 224 genes with differential DNA methylation persons in epilepsy patients and healthy people(Wang et al., 2016b). In the epileptic samples, three genes (*TUBB2B, ATPGD1, HTR6*) exhibited relative transcriptional regulation by DNA methylation. *TUBB2B* and *ATPGD1* showed hypermethylation and reduced mRNA levels, while *HTR6* showed hypomethylation and increased mRNA levels(Wang et al., 2016b). These findings suggest that some genes are differentially regulated by DNA methylation in human epilepsy. Previous studies have shown that 27 hypomethylated genes and 119 hypermethylated genes are present in hippocampal tissue from patients with DR-TLE compared with healthy people(Miller-Delaney et al., 2015). Meanwhile, DNMT1 and DNMT3a are highly expressed in the temporal neocortex of DR-TLE patients, which are involved in DNA methylation(Zhu et al., 2012). The lower levels of global DNA methylation and the lower expression of DNMT3a2 were found in the hip-

pocampus of TLE. Interestingly, compared with control and TLE groups, the expression of DNMT3a1 and DNMT3a2 was more significant reduced in the hippocampus of TLE with febrile seizures (FS) history(de Nijs et al., 2019). Mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS) is the most common focal epilepsy, which characterized by strong drug resistance. In the intracortical KA-induced mouse models of mTLE-HS, contralateral hippocampus (CLH) shows substantial changes in gene expression and DNA methylation in glia and neurons, in which some genes and pathways associated with antiepileptic effects were upregulated(Berger et al., 2020). Although changes of gene expression in CLH and ILH overlap to a large extent, changes of DNA methylation were not overlapped(Berger et al., 2020). As the seizures last longer, DNA methylation of many genomic sites is significantly changed, and progression of epilepsy is also relevant to changes in DNA methylation of inflammatory-related genes(Martins-Ferreira et al., 2021). Therefore, seizures may be responsible for altered DNA methylation of certain genes(Caramaschi et al., 2020). And changes of DNA methylation may also contribute to the development of epilepsy.

At present, the regulation of synaptic function in epilepsy may also have light with DNA methylation of related genes. Relevant studies have shown that DNA methylation-dependent endocytosis may be involved in the regulation of synaptic function in inhibitory cortical interneurons of mice, which have potential significance in TLE(Pensold et al., 2020). Moreover, synaptic NMDAR expression is also regulated by DNA methylation. Related study has found that activated NMDAR-containing GluN2A subunits control DNMT3a1 levels in neurons and drive degradation of DNMT3a1 in a ubiquitin-like dependent manner, which may be associated with synaptic plasticity and memory formation(Bayraktar et al., 2020). At the same time, the upregulation of DNMT3b expression is also regulated by NO produced by NMDAR activation in the hippocampus(de Sousa Maciel et al., 2020). Moreover, glutamate dysfunction and cognitive decline are also closely associated with changes in *GRIN2B*promoter methylation(Fachim et al., 2019). Overexpression of DNMT1 in ES cells leads to epigenetic changes, which results in abnormal neuronal differentiation with upregulated functional NMDARs(D'Aiuto et al., 2011). SE can trigger early and late changes of *BDEF* and*GRIN2B* DNA methylation levels in the hippocampus(Ryley Parrish et al., 2013). In the epileptic hippocampus, increased levels of*GRIN2B* DNA methylation lead to decreased expression of GluN2B and decreased levels of *BDNF* DNA methylation also result in increased expression of BDNF. Meanwhile, inhibition of DNMT can decrease*GRIN2B* mRNA expression and increase excitatory postsynaptic potential in hippocampus of epileptic rats(Ryley Parrish et al., 2013).

The blocking of DNA methylation may play an important role in epileptogenesis and treatment of epilepsy. Abnormal DNA methylation of*RASgrf1* is closely associated with epilepsy. RG108 as a DNMT inhibitor, can block hypermethylation of the *RASgrf1* promoter and inhibited acute epileptic activity in the KA-induced epilepsy models(Chen et al., 2017). The high-dose 5-Aza-2dC as a DNMT inhibitor, significantly increase seizure threshold and attenuate seizures in PTZ-kindled model of rats, which suggesting inhibited DNMT activity can reduce epilepsy acquisition and seizure susceptibility(Williams-Karnesky et al., 2013). Adenosine intervention can reverse DNA hypermethylation in the epileptic brain, thereby inhibiting sprouting of mossy fibers in the hippocampus and preventing the progression of epilepsy in a rat model of TLE(Williams-Karnesky et al., 2013). Studies have shown that methylation level of *EPHX1* promoter is significantly correlated with epilepsy that is resistant to carbamazepine (CBZ). *EPHX1*methylation may be a potential target of CBZ treatment and a potential marker of DREs for CBZ (Lv et al., 2019). Elevated levels of matrix metalloproteinase-9 (MMP-9) have been implicated in epileptogenesis of humans and animals. Upregulated MMP-9 expression is primarily regulated by deletion of MMP-9 gene proximal promoter including interweaved potent silencing mechanisms-DNA methylation and polycomb repressive complex 2 (PRC2)-related repression(Zybura-Broda et al., 2016). In addition, DNA demethylation has also been reported to depend on the gradual dissociation of DNMT3a and DNMT3b, as well as the progressive binding of DNA demethylation promoter Gadd45β to the MMP-9 proximal gene promoter in vivo(Zybura-Broda et al., 2016). These studies identify MMP-9 expression is regulated by DNA methylation in human epilepsy.

In conclusion, DNA methylation is involved in the occurrence and treatment of epilepsy. However, the regulatory mechanism of DNA methylation in epilepsy is still not completely clear and needs further exploration.

2.2 Histone modifications

Currently, histone tails and globular domains contain multiple targets of several posttranslational modifications, such as ubiquitination, phosphorylation, acetylation, methylation and ADP-ribosylation. Previous studies have supported that epilepsy and seizures can induce histone modifications and histone modifications also influence epileptogenesis. Therefore, we will focus on the roles of histone acetylation and histone methylation in epilepsy.

2.2.1 Histone acetylation

Histone acetylation modifying enzymes regulate transcription process by changing the status of histone acetylation in chromosomes(Riaz et al., 2015). Histone deacetylases (HDACs) and histone acetyltransferases (HATs) are necessary to maintain epigenetic regulation of gene expression by histone acetylation. HATs catalyze the reversible acetylation reaction at the ε-amino group of lysine residues. Chromatin relaxation and increased transcriptional activity of genes is associated with neutralization of the positive charge of lysine residues by histone acetylation. Meanwhile, HDACs can remove acetyl groups silencing the transcriptional activity of genes and leading to chromatin condensation**(Figure2)** (Wawruszak et al., 2021). HDACs are divided into four main classes: Class I (HDACs 1, 2, 3,8), Class IIa (HDAC4, 5, 7, 9) and Class IIb (HDAC6, 10), Class III (SIRT1-SIRT7), Class IV (HDAC11) (Wawruszak et al., 2021). HDACs (Class I, II and III) share sequence similarity and require Zn^{2+} for deacetylase activity. However, SIRT1-7(class III), show no sequence resemblance to members of the classical family and require NAD^{+} as the cofactor(Gregoretti et al., 2004; Whittle et al., 2007). In the HDAC family, classes I and II are most associated with epilepsy, and have been found to have the highest expression in the brain(Younus and Reddy, 2017). In the CNS, HDAC2 is thought to inhibit memory consolidation and synaptic plasticity by inhibiting HDAC acetylation and HDAC5 is also critical to memory formation(Younus and Reddy, 2017). HDAC6 plays a neuroprotective role by promoting autophagy of damaged proteins(Boyault et al., 2007). However, HDAC6 is also involved in regulating the function of microtubule networks and impairs neuronal axon transport(d'Ydewalle et al., 2012). In addition, the biological functions of HDACs are also involved in metabolism, protein degradation, angiogenesis, DNA damage, immune regulation, cell cycle and apoptosis.

In patients and animal models of epilepsy, changes of histone acetylation have attracted widespread attention and have been considered to be involved in epileptogenesis(Hauser et al., 2018; Boison and Rho, 2020). Relevant studies have shown that seizures promote deacetylation of histone H4 of GluR2, which is closely related to epileptogenesis and increased neuronal excitability(Huang et al., 2002; Tsankova et al., 2004; Chen et al., 2021b). In a model of Tuberous Sclerosis Complex (TSC) of mouse, histone H3 acetylation (H3K9Ac and H3K27Ac) levels are generally decreased in the hippocampal neurons. Inhibition of HDAC activity can restore histone H3 acetylation levels and improve abnormal synaptic plasticity and seizure threshold in TSC2, which suggesting HDAC inhibitors may be novel therapeutic strategies for TSC(Basu et al., 2019). Multiple studies reported increased H3 phosphorylation in pilocarpine and KA-induced seizures, which is believed to promote the underlying mechanism that induces histone acetylation(Younus and Reddy, 2017). Furthermore, increased histone H4 acetylation is also reported in pilocarpine, KA and electroconvulsive-induced epilepsy models(Huang et al., 2002; Tsankova et al., 2004; Sng et al., 2006). Altered histone acetylation at *GluR2* and *BDNF* genes is an early event triggered by SE. Meanwhile, increased histone H4 acetylation is also linked to upregulated BDNF and c-FOS/c-JUN genes(Huang et al., 2002). Related studies have shown that the downregulation of c-FOS transcription may be achieved by histone H4 acetylation, while the upregulation of BDNF transcription may be related to the regulation of histone H3 acetylation(Tsankova et al., 2004).

Currently, several HDACs are upregulated during epilepsy. In the brain tissue of patients with DR-TLE, HDAC2 is upregulated, which is associated with reduced histone acetylation and gene expression. HDAC4 downregulates the gene expression of $GABA_A$ α1 subunit and AMPAR subunit GluA2, which suggesting that decreased $GABA_A$ α1 subunit and downregulated AMPAR subunit GluA2 are associated with histone deacetylation after seizures(Fonseca-Barriendos et al., 2021). In addition, mutations in the factor-induced-gene 4 (FIG4) gene are associated with multiple disorders including epilepsy. Defects of HDAC1 may also explain FIG4-associated disorders including epilepsy(Muraoka et al., 2021). Moreover, the trans-

formation/transcription domain-associated protein (TRRAP) is a common component of many HAT complexes(Leduc et al., 2014). Some results demonstrate TRRAP-dependent histone acetylation plays an essential role in regulating neurogenesis and cell cycle(Tapias et al., 2014). Meanwhile, it has been found that mutations of TRRAP can also cause human neuropathies including epilepsy. In addition, TRRAP regulates microtubule dynamics through the SP1 signaling pathway to prevent neurodegeneration(Tapias et al., 2021).

In epilepsy, some drugs, including ADEs, also regulate histone acetylation. Blocking HDACs with specific inhibitors appears to be an effective therapeutic strategy for enhancing neuroprotection and interfering with epileptogenesis(Boison and Rho, 2020). Ketogenic diet (KD), as an important treatment for epilepsy, can enhance the production of β-hydroxybutyrate which is a HDAC inhibitor(Lusardi et al., 2015; Longo et al., 2019). Traumatic brain injury (TBI) is an important cause of epileptogenesis. Related study has found that inhibition of HDAC can improve learning and memory after TBI by combining with behavioral therapy (Dash et al., 2009). Meanwhile, HDAC inhibitor ITF2357 has neuroprotective effects and promotes neurological function recovery following TBI(Shein et al., 2009). In addition, HDAC inhibitor can also promote histone H3 acetylation and inhibt inflammatory response of microglia following TBI in rats(Zhang et al., 2008). Valproic acid (VPA), the most common AED, is known to suppress seizures by increasing levels of GABA in the brain. Meanwhile, VPA is also a well-known HDAC inhibitor(Lunke et al., 2021; Wawruszak et al., 2021). VPA regulates histone acetylation together with HATs, suggesting that epigenetic regulation of genes by VPA may be involved in the occurrence of neurological diseases(Hu et al., 2020b). Relevant study has shown that VPA may also participates in epileptogenesis by regulating HDACs(Hu et al., 2020b). The study has found that the inhibitory concentration of VPA on HDACs activity is about 0.3-1.0mM, which is within the therapeutic range of VPA in human epilepsy(Blaauboer et al., 2022). Both class I and class II HDACs are inhibited by VPA, with the highest potency for class I HDACs, especially HDAC1(Phiel et al., 2001; Blaauboer et al., 2022). The epigenetic effects of VPA mainly depend on inhibition of HDACs and regulation of BDNF(Ghiglieri et al., 2010). VPA and Other HDAC inhibitors can downregulate TrkB expression and BDNF/TrkB signaling(Dedoni et al., 2019). Meanwhile, VPA is also involved in inflammatory response by inhibiting of HDACs. VPA can mitigate traumatic spinal cord injury-induced inflammation response by HDAC3-dependent STAT1 and NF-κB pathway(Chen et al., 2018). In addition, sodium butyrate, a critical HDAC inhibitor in the aliphatic fatty acid family, can increase histones H3 and H4 acetylation in the hippocampus and cerebral cortex of mice(Younus and Reddy, 2017). Sodium butyrate can also improve the anticonvulsant activity of MK-801 (dizocilpine), an NMDAR antagonist(Deutsch et al., 2008). Sodium butyrate has been shown to modulate the effects of AED flurazepam to antagonize electrically precipitated seizures(Deutsch et al., 2009). Meanwhile, sodium butyrate significantly delays epileptogenesis, delays the development of seizures and reduces the severity of behavioral seizures in mice(Younus and Reddy, 2017). In the hippocampus kindling model of TLE, sodium butyrate significantly inhibited HDAC activity and retarded the development of limbic epileptogenesis. Meanwhile, inhibition of HDAC can significantly reduce persistent seizures, eliminate the epileptic state, and significantly reduce the sprouting mossy fiber(Reddy et al., 2018). Histone H3 and H4 acetylation levels are decreased in epileptic rats, while histone acetylation levels is significantly increased when treated with sodium butyrate or VPA alone in the brain, especially combined administration(Citraro et al., 2020). These findings suggest that sodium butyrate has a strong antiepileptic effect by regulating HDACs.

In a word, these findings support the underlying theory that HDAC inhibitors prevent epilepsy by interfering with epigenetic gene expression profiles. Importantly, histone acetylation modifications may have a crucial role in epileptogenesis and early treatment with HDAC inhibitors might be a possible strategy for preventing epileptogenesis.

2.2.1 Histone methylation

Histone methylation, is a unique post-translational modification catalyzed by histone methyltransferases (HMTs), which occurs mainly on lysine (K) and arginine (R) residues. Key enzymes involved in histone methylation include HMTs and histone lysine demethylase (KDMs)(Jin et al., 2022). Lysine methylation occurs in mono-, di-, and tri-states, whereas arginine methylation only occurs in monoand di-states. Histone

H3 methylation occurs at lysine residues K4, K9, K27, K36, and K79 and histone H4 methylation occurs at lysine residues K20(Jin et al., 2022). Most studies have found that H3K9me2/me3, H3K27me2/me3 and H4K20me3 frequently occur on gene silenced heterochromatin(Vermeulen et al., 2010). In general, methylation at H3K9, H3K27, and H4K20 is associated with transcriptional inhibition, while methylation at H3K4, H3K36, and H3K79 is associated with gene transcription(Hon et al., 2009). Currently, there are two main families of histone demethylases, including lysine-specific demethylases (LSDs) and Jumonji C (JmjC) domain-containing lysine demethylases (JmjC-KDMs)(Jin et al., 2022). Related study has found that both LSD1 and LSD2 function as corepressors marks on H3K4 through the demethylation of mono- or di-methyl (Han et al., 2019). However, LSD1 may also be as a coactivator of androgen receptors by the demethylation of H3K9me1/me2(Metzger et al., 2005). In addition, the members of the JmjC-KDM family are mainly responsible for the demethylation of H3K4, H3K9, H3K27, H3K36, H3K79 and H4K20 through cosubstrate2-oxoglutarate, dioxygen and Fe (II) as cofactors(Labbé et al., 2013; Jin et al., 2022).

In the diseases of CNS, an association between between the severity of intellectual disability and the dysregulation in the KDM5C-H3K4me3 pathway has been reported in neurodevelopmental disorders (NDDs)(Poeta et al., 2021). Meanwhile, KDM5C variants are resulted in neuropsychiatric symptoms, such as epilepsy, delayed development of language and intellectual disability(Wei et al., 2016). In addition, the development of intellectual disability and Rett syndrome has also been found to be associated with mutations of JMJC-KDM (Sáez et al., 2016). Recent studies have shown that histone methylation is also involved in the pathogenesis and treatment of epilepsy. Setdb1, as the member of the H3K9 HMT family, is widely expressed in the developmental brain and is related to the inhibition of chromatin remodeling by targeting histone H3K9 residues(Jiang et al., 2010). The inhibition of Setdb1-mediated histone methylation of *GRIN2B* is related to the decreasing of GluN2B expression(Jiang et al., 2010). It has also been found that SETD1B, as an important component of the HMT complex, is involved in epigenetic regulation of chromatin structure and gene expression by specifically methylating histone H3K4(Krzyzewska et al., 2019). However, SETD1B variants are related to autism, intellectual disability and epilepsy. Meanwhile, SETD1B variants also contribute to a number of clinical phenotypes, including variable epileptic phenotypes, delayed language and delayed global development(Hiraide et al., 2018; Weerts et al., 2021). LSD1 is a commonly expressed histone H3K4 demethylase that acts as a transcription corepressor together with CoREST and HDAC1/2(Rusconi et al., 2015). In a mouse epilepsy model, LSD1/KDM1A can regulate neuronal excitability by neural-specific alternative splicing(Rusconi et al., 2015). In addition, specific deletion of neuroLSD1 in mice showed hypoexcitable and reduced susceptibility to epilepsy(Rusconi et al., 2015). Related research has found that H3K9me2 and its enzyme euchromatic histone-lysine-methyltransferase 2 (G9a) affect transcriptional regulation of the potassium channel 10 (Kcnj10) gene which encodes the Kir4.1 channel and are sensitive to epileptic seizure activity in epileptic rats(Zhang et al., 2018c).

These findings suggest that the regulation of histone methylation may provide new research directions for the pathogenesis and treatment of epilepsy. However, the mechanism of histone methylation regulation in epilepsy is not completely clear and needs to be further explored in the future.

2.3 Noncoding RNAs (ncRNA)

NcRNAs which include small (microRNA) and long (lncRNA), play a crucial role in regulating gene expression. Bioinformatics analysis have found that abnormal methylation of lncRNAs and microRNAs are associated with neurotrophic factor signaling pathway, MAPK signaling pathway, drug metabolism and ion channel activity (Xiao et al., 2018). In addition, aberrantly methylation of ncRNAs may be involved in development and progression of TLE(Xiao et al., 2018). NcRNAs are highly selectively targeting and may play an important role in epilepsy, but their role in refractory epilepsy still needs to be explored further. Thus, we will discuss microRNAs and lncRNAs.

2.3.1 MicroRNA

MicroRNAs can be detected in biological fluids, making them potential diagnostic biomarkers, which have been reported as biomarkers for the diagnosis of epilepsy. Meanwhile, microRNA, as an emerging thera-

peutic target, provides unique therapeutic advantages for some epilepsy with complex pathophysiological mechanisms by negatively regulating related proteins(Morris et al., 2021). Currently, many microRNAs are consistently dysregulated in epilepsy and affect seizures, which are also described as biomarkers for the diagnosis of TLE and predictive biomarkers for AED response(Mooney et al., 2016; De Benedittis et al., 2021) **(Table1)** .

Related studies have found that microRNAs are significantly upregulated in epilepsy. MicroRNA-20a-5p is involved in synaptic plasticity and silencing microRNA-20a-5p inhibits neuronal branching and axonal growth and prevents epileptogenesis by regulating RGMa-RhoA-mediated synaptic plasticity in the PTZ-induced epilepsy model(Feng et al., 2020). MicroRNA-21-5p reduces IL-6 levels, loss of hippocampal neurons and apoptosis by inhibiting STAT3 expression, which suggesting protective effects of microRNA-21-5p in hippocampal neurons of epileptic rats(Zhang et al., 2020). In KA-induced SE models, targeting of microRNA-21-5p also protects against seizure-induced injury by PTEN-mTOR (Tang et al., 2018). MicroRNA-23a is involved in hippocampal neuron injury, hippocampal oxidative damage and impairment of spatial memory in KA-induced TLE mice(Zhu et al., 2019b). Meanwhile, microRNA-23a can also regulate ADAM10, which contributes to epileptogenesis in pilocarpine-induced SE mice(Zhu et al., 2019a). MicroRNA-27a-3p regulates ion channel-related DEGs in multiple mTLE and downregulation of microRNA-27a-3p inhibits apoptosis of hippocampal neurons and inflammatory response by upregulating MAP2K4 in KA-induced epilepsy models(Lu et al., 2019; Su et al., 2022b). Inhibition of microRNA-103a regulates BDNF to improve neuron injury and inhibit activated astrocytes in pilocarpine-induced epilepsy rat models(Zheng et al., 2019). Depletion of microRNA-132 can reduce seizure-induced neuronal death in KA-induced epilepsy mice models and microRNA-132 can suppress BDNF/TrkB signaling to aggravate epileptiform discharges in the Mg^{2+}-free treated hippocampal neuronal model of SE(Jimenez-Mateos et al., 2011; Xiang et al., 2015). Meanwhile, microRNA-132 also reduces the expression of pro-epileptogenic factors (COX-2, IL-1β, TGF-β2, CCL2 and MMP3) in human cultured astrocytes of TLE(Korotkov et al., 2020). Inhibition of microRNA-134 can effectively reduce the occurrence of spontaneous recurrent seizures and silencing microRNA-134 can produce neuroprotective, reducing the severity of seizures in KA-induced epilepsy mice model(Jimenez-Mateos et al., 2012; Morris et al., 2019). MicroRNA-134 inhibits the expression of cAMP-response element binding protein (CREB) and p-CREB to regulate synaptic plasticity in pilocarpine-induced epilepsy rat model(Zhu et al., 2015). Antagonizing microRNA-135a can reduce spontaneous recurrent seizures to affect synaptic function and plasticity by targeting Mef2a in KA-induced epilepsy mice model. And inhibition of microRNA-135a protects glial cells against apoptosis by regulating SIRT1-related signaling pathway in KA-induced BV2 microglia epilepsy model(Vangoor et al., 2019; Wang et al., 2021c). Inhibition of microRNA-141 can inhibit P53 to protect against apoptosis by SIRT1 expression in KA-induced epilepsy rat model(Liu et al., 2019a). MicroRNA-142 performs well in differentiating between drug-resistant and drug-sensitive TLE. Inhibition of microRNA-142 promotes mitochondrial autophagy and reduces hippocampal neuron damage by targeting PINK1 in pilocarpine-induced epilepsy rat model(Xiao et al., 2021). Downregulation of microRNA-145 improves the abilities of learning and memory by reducing apoptosis of hippocampal neurons in pilocarpine-induced epilepsy rat model(Zhao et al., 2019a). MicroRNA-146a is a powerful regulator of microglia-mediated inflammation in the chronic TLE(Aronica et al., 2010; Su et al., 2016). MicroRNA-146a-CFH-IL-1β loop circuit mediates the perpetuate inflammation of chronic TLE in KA-induced epilepsy rat model and antagonists targeting microRNA-146a can also protect against SE by regulating NF-ϰB pathway in pilocarpine-induced epilepsy rat model(Li et al., 2018c; Zhang et al., 2018a). In addition, microRNA-146a can ameliorate dysregulation of the MMP/TIMP proteolytic system in TSC(Broekaart et al., 2020). Febrile seizure(FS)-related microRNA-148a-3p plays neuroprotective roles by increasing the proliferation of hippocampal neurons in Mg^{2+} -free medium treated TLE cell model(Yu et al., 2021). MicroRNA-155 is involved in epileptogenesis by the PI3K/Akt/mTOR signaling pathway(Duan et al., 2018). Meanwhile, inhibition of microRNA-155 attenuates MMP3 expression in cultured human astrocytes, increases the expression of BDNF and alleviates seizure severity in the pilocarpine-induced epilepsy, and attenuates KA-induced seizure by inhibiting microglia activation(Cai et al., 2016; Korotkov et al., 2018; Fu et al., 2019). MicroRNA-181b can inhibit P38/JNK signaling pathway by targeting TLR4, thereby reducing apoptosis and autophagy in KA-induced epilepsy rat model(Wang et al., 2019b). However, inhibition of microRNA-181a-5p also activates SIRT1

to reduce neuronal apoptosis, neuroinflammation, oxidative stress, cognitive dysfunction and activation of astrocyte and microglia in pilocarpine-induced epilepsy rat model(Kong et al., 2020). Downregulated microRNA-183 results in an inactivation of JAK/STAT signaling pathway by targeting Foxp1 to promote neuron proliferation and inhibit apoptosis of hippocampal neurons, thereby attenuating hippocampal neuron injury in pilocarpine-induced epilepsy rat model(Feng et al., 2019). MicroRNA-187-3p is upregulated and regulates KCNK10/TREK-2 potassium channel in electrical stimulation-induced SE(Haenisch et al., 2016). MicroRNA-194-5p regulates the proliferation and apoptosis of hippocampus neuron in children with TLE and Mg^{2+} -free medium treated epilepsy cell model (Niu et al., 2021). Targeting of microRNA-199a-5p protects against neuron damage by SIRT1-p53 cascade in pilocarpine-induced epilepsy rat model (Wang et al., 2016a). Downregulation of microRNA-200c-3p upregulates RECK and inactivates the AKT signaling to decrease apoptosis of hippocampal neuron in pilocarpine-induced epilepsy rat model(Du et al., 2019). MicroRNA-203 is targeted to Ppp2ca in both humans and mice, which can target Ppp2ca to increase seizure activity in the KA-induced SE model(Zhang et al., 2018b). And microRNA-203 antagomirs can targets glycine receptor-β(GLRB) to decrease the frequency of spontaneous seizures in pilocarpine-induced mice epilepsy(Lee et al., 2017). MicroRNA-219 regulates NMDARs in the amygdala and hippocampus of patients with mTLE and also suppresses seizure formation by regulating the CaMKII/NMDAR pathway in KA-induced epilepsy mice model(Zheng et al., 2016; Hamamoto et al., 2020). MicroRNA-223 also have the good performance in distinguishing drug-sensitive and drug-resistant TLE and microRNA-223 affects microglial autophagy by targeting ATG16L1 in TLE(De Benedittis et al., 2021; He et al., 2021b). MicroRNA-451 regulates GDNF expression to aggravate hippocampal neuronal apoptosis and seizure in KA-induced epilepsy mice model(Weng et al., 2020).

Related studies have also found that microRNAs are significantly downregulated in epilepsy. MicroRNA-15a targets GFAP to inhibit inflammation and apoptosis of hippocampal neurons by downregulating GFAP in pilocarpine-induced epilepsy rat model and Mg^{2+}-free medium treated TLE cell model(Fan et al., 2020). Propofol regulates microRNA-15a-5p/GluN2B/ERK1/2 pathway to suppress apoptosis hippocampal neuronal apoptosis in Mg^{2+} -free medium treated epilepsy cell model (Liu et al., 2020). MicroRNA-22 inhibits neuroinflammatory signaling to protect against the development of epileptogenic brain networks. MicroRNA-22 prevents inflammation and development of epileptogenic focus by targeting P2X7R in the brain and microRNA-22 regulates aberrant neurogenesis and changes in neuronal morphology after SE in KA-induced epilepsy mice model(Jimenez-Mateos et al., 2015; Beamer et al., 2018; Almeida Silva et al., 2020). MicroRNA-25-3p targets OXSR1 to suppress oxidative stress and apoptosis of neurons, thereby suppressing epileptiform discharges in KA-induced epilepsy mice model(Li et al., 2020). MicroRNA-29a regulates seizure-induced cell death and inflammation in Mg^{2+}-free medium treated epilepsy cell model(Wu et al., 2021). Activated microRNA-34a may lead to impaired corticogenesis in TSC during early brain development and inhibition of microRNA-34a can regulate apoptosis and Notch signaling to inhibit epileptiform discharges in Mg^{2+}-free medium treated epilepsy cell model(Wang et al., 2019a; Korotkov et al., 2021). Meanwhile, microRNA-34c plays a negative role in seizure and cognitive function by regulating NMDARs and AMPARs in PTZ-induced epilepsy rat model(Huang et al., 2018). In addition, decreased microRNA-34c-5p enhances neuroinflammation to increase loss of hippocampal neuron in DRE from KA-induced epilepsy mice model and in children with DRE(Fu et al., 2020). MicroRNA-101a-3p inhibits apoptosis and autophagy by downregulating c-FOS in pilocarpine-induced epilepsy rat model and Mg^{2+}-free medium treated epilepsy cell model(Geng et al., 2021). MicroRNA-124 inhibits some target genes to prevent upregulation of hippocampal NRSF, which participates in epilepsy and promotes the activation of hippocampal microglia and inflammatory cytokines(McClelland et al., 2014; Brennan et al., 2016). MicroRNA-124 suppresses seizure, regulates CREB1 activity, and inhibits neuronal firing with decreased expression of NMDAR in pilocarpine and PTZ-induced epilepsy rat model(Wang et al., 2016c). MicroRNA-125a-5p targets CaMK4 to alleviate dysfunction and inflammation in PTZ-induced epilepsy rat model(Liu et al., 2019b). Inhibition of microRNA-129-2-3p regulates GABRA1 to protect against refractory TLE in KA-treated primary hippocampal neurons and KA-induced epilepsy rat model(Wang et al., 2021a). MicroRNA-129-5p also targets HMGB1 to inhibit the development of autoimmune encephalomyelitis-related epilepsy by TLR4/NF-kB pathway(Liu et al., 2017a). MicroRNA-136 inhibits WNT/-Catenin signaling pathway to play a neuroprotective effect on

pilocarpine-induced TLE rats (Cui and Zhang, 2022). Overexpression of microRNA-137 inhibits seizure activity in two different epilepsy mouse models (PTZ and pilocarpine) and suppresses neuronal excitability in Mg^{2+}-free-induced brain slice model of epileptiform activity(Wang et al., 2018b). MicroRNA-139-5p negatively regulates GluN2A-NMDAR in pilocarpine-induced epilepsy rat model and TLE patients and upregulated microRNA-139-5p also regulates the Notch pathway to reduce spontaneous recurrent epileptiform discharge-induced apoptosis and oxidative stress in rat primary hippocampal neurons(Alsharafi et al., 2016; Zhao et al., 2021). MicroRNA-153 is downregulated in plasma and temporal cortex of mTLE patients and overexpression of microRNA-153 reduces HIF-1α expression in rat astrocytes of refractory epilepsy(Li et al., 2016). MicroRNA-204 regulates TrkB-ERK1/2-CREB signaling to inhibit epileptiform discharges in Mg^{2+}-free medium cultured hippocampal neurons(Xiang et al., 2016). Dynamic changes of microRNA-211 expression is associated with epileptiform activity and cholinergic imbalances in murine forebrain(Bekenstein et al., 2017). MicroRNA-221-3p inhibits HIF-1α to suppress seizures and microglia activation in the VPA-resistant epilepsy of KA-induced epilepsy mice model(Fu et al., 2021). MicroRNA-322-5p regulates the TLR4/TRAF6/NF-κB axis to reduce neuronal inflammation in pilocarpine-induced epilepsy rat model(Zhou et al., 2022). MicroRNA-344a regulates seizure-induced apoptosis signaling pathways in PTZ-induced chronic epilepsy rat model (Liu et al., 2017b). Overexpressed microRNA-494 inactivates the NF-κB signaling pathway to reduce hippocampal neuron injury by inhibiting RIPK1 in pilocarpine-induced epilepsy rat model(Qi et al., 2020). MicroRNA-542-3p suppresses TLR4/NF-κB signaling pathway to reduce seizure-induced brain injury and the expression of P-gp in KA-treated primary hippocampal neurons and KA-induced epilepsy rat model(Yan et al., 2019). Oddly, microRNA-128 is significantly downregulated at various phases of TLE development in epilepsy rat models and TLE patients(Tan et al., 2013; Alsharafi and Xiao, 2015). However, it has been found that microRNA-128 is upregulated in KA-induced epilepsy rat model and promotes apoptosis by the SIRT1 cascade in PC12 cells(Chen et al., 2019). MicroRNA-128 can inhibit the expression of various ion channels and the signaling of ERK2 network that regulate neuronal excitability. Meanwhile, microRNA-128 also inhibits SNAP-25 and SYT1 expression to regulate epilepsy sensitivity in KA-induced epilepsy mice model(Wang et al., 2021b). In addition, microRNA-378, microRNA-575, microRNA-629-3p, microRNA-1202, microRNA-1225-5p, and microRNA-138-5p may also be diagnostic indicators and predicting surgical prognosis in human epilepsy(Gattás et al., 2022; Li et al., 2022; Ünalp et al., 2022).

In a word, these novel biomarkers may help to identify new epileptic treatment targets and contribute to improved epileptic patients' quality of life through earlier diagnosis and a more precise prognosis.

2.3.2 lncRNA

LncRNAs are a class of long transcripts that do not have protein-coding ability, which have become regulatory molecules widely involved in biological processes(Villa et al., 2019). Increasing evidences indicate that lncRNAs are associated with RNA processing, the control of nuclear organization and transcriptional and post-transcriptional regulation of gene expression (Yao et al., 2019). LncRNAs, as competitive endogenous RNAs (ceRNAs), competitively suppress microRNAs to regulate transcription of RNAs(Chen et al., 2021a). Moreover, lncRNAs are involved in multiple biological processes, such as cell death, immuno-inflammatory responses, proliferation, organogenesis, genomic imprinting and chromatin remodeling (Fernandes et al., 2019). LncRNAs have been also implicated in several human diseases, such as neurological disorders, autoimmune disease, cardiovascular disease, metabolic disease and cancer (Hu et al., 2018; Villa et al., 2019). In the CNS, some lncRNAs may play key roles in neuronal function, development and maintenance of memory, cognitive function and synaptic plasticity(Wu et al., 2013). More and more studies believe that regulation of lncRNAs is closely related to epilepsy, which may become the prospect of new therapeutic interventions for epilepsy(Irwin et al., 2021).

In epilepsy, many studies have reported that lncRNAs are dysregulated in epilepsy and are involved in the pathological process of epilepsy**(Table2)** (Villa et al., 2019). Abnormal expression of lncRNAs has been found in both epileptic animal models and epileptic patients(Lee et al., 2015; Jang et al., 2018; Xiao et al., 2018). In pilocarpine-induced epileptic mouse model, the differentially expressed lncRNAs are unique in each brain region(Jang et al., 2018). It has been found that occurrence and progression of TLE is closely related

to the changed methylation profiles of lncRNAs. In this study, 384 lncRNAs are significantly dysregulated in pilocarpine-induced epileptic model and 279 lncRNAs are significantly dysregulated in KA-induced epileptic model(Lee et al., 2015). Hypermethylated lncRNAs are associated with drug metabolism ion channel activity, GABAR activity and synaptic transmission, suggesting that lncRNAs may be involved in the mechanism of refractory mTLE(Xiao et al., 2018).

BDNF antisense RNA (BDNF-AS; BDNF-OS), is a lncRNA transcribed from the opposite strand of *BDNF* (Lipovich et al., 2012). Study has found that BDNF-AS levels are significantly decreased and BDNF expression is significantly increased in human neocortex of intractable epilepsy(Lipovich et al., 2012). Meanwhile, that BDNF-AS can negatively regulate the expression of BDNF has also been confirmed in vitro(Modarresi et al., 2012). Thus, regulation of BDNF by BDNF-OS may be as a treatment for intractable epilepsy. New evidence has revealed that lncRNAs mainly serve as ceRNA targeting microRNAs in regulating neuronal apoptosis. LncRNA H19 suppresses microRMA-let-7b to regulate hippocampal neuron apoptosis and lncRNA H19 also regulates JAK/STAT signaling to promote activation of hippocampal glial cell in TLE rat model(Han et al., 2018a; Han et al., 2018b). LncRNA FTX regulates microRNA-21-5p/SOX7 axis to suppress apoptosis of hippocampal neurons in a rat model of TLE(Li et al., 2019b). Meanwhile, LncRNA GAS5 inhibits microRNA-219 to affect CaMKIIγ/NMDAR pathway and promote the progression of epilepsy(Zhao et al., 2022). However, lncRNA GAS5 silencing regulates microRNA-135a-5p to suppress the expression of KCNQ3, thereby preventing the progression of epilepsy(Li et al., 2019a). LncRNA TUG1 may be a biomarker of TLE diagnosis in children, and regulates miR-199a-3p to affect cell activity and apoptosis of hippocampal neuron (Li et al., 2021). LncRNA UCA1 regulates microRNA-495/Nrf2-ARE signal pathway to suppress seizure-induced brain injury and seizure, and lncRNA-UCA1 has dynamic regulation effect on NF-κB in hippocampus of epilepsy rats(Wang et al., 2017; Geng et al., 2018). Meanwhile, lncRNA UCA1 regulates microRNA-375/SFRP1-mediated WNT/β-Catenin pathway to alleviate aberrant hippocampal neurogenesis in KA-induced epilepsy model (Diao et al., 2021). LncRNA UCA1 regulates microRNA-203-mediated MEF2C/NF-κB signaling pathway to inhibit inflammation in epilepsy(Yu et al., 2020). LncRNA ILF3-AS1 suppresses microRNA-212 to mediate epileptogenesis in the hippocampus and targets microRNA-212 to promote the expression of inflammatory cytokines and MMPs in TLE(Cai et al., 2020). Previous studies have confirmed that lncRNA NEAT1 is responsive to neuronal activity and is associated with hyperexcitability states. However, LncRNA NEAT1 also targets microRNA-129-5p and regulates Notch signaling to regulate inflammatory responses in epilepsy (Barry et al., 2017; Wan and Yang, 2020). LncRNA XIST sponges miR-29c-3p and regulates NFAT5 expression to promote the secretion of inflammatory cytokines in LPS-treated CTX-TNA2(Zhang et al., 2021). LncRNA Nespas, as a regulator of microRNA-615-3p, inhibits the PI3K/Akt/mTOR pathway to suppress apoptosis of epileptiform hippocampal neurons by upregulating Psmd11(Feng et al., 2021). SP1 activated-lncRNA SNHG1 regulates microRNA-154-5p/TLR5 axis to mediate the development of epilepsy(Zhao et al., 2020). LncRNA ZFAS1 upregulates microRNA-421 to activate the PI3K/AKT pathway, thereby inhibiting apoptosis and autophagy of hippocampal neurons in epilepsy(Hu et al., 2020a). Meanwhile, lncRNA ZFAS1 can also promote neuronal apoptosis and inflammation response, thereby aggravating the development of epilepsy(He et al., 2021a). These regulation mechanisms of lncRNAs in epilepsy and seizure-induced brain injury by targeting microRNAs may provide new targets for biological therapy of epilepsy. Silencing lncRNA PVT1 can downregulate WNT signaling pathway to promote the expression of BDNF and suppress the activation of hippocampal astrocytes in epileptic rats(Zhao et al., 2019b). Related research has found that MALAT1 can regulate the density of dendritic spines, and loss of lncRNA BC1 can reduce the convulsion thresholds(Murugan and Boison, 2020). Downregulated lncRNA MALAT1 regulates the PI3K/Akt signaling pathway to protect hippocampal neurons against excessive autophagy and apoptosis in rats with epilepsy(Wu and Yi, 2018). In addition, lncRNA KCNH5-1 plays a key vital role in developing TLE with hippocampal sclerosis (HS)(Wang et al., 2022).

In addition, circular RNAs (circRNAs) are a class of lncRNAs with a closed loop structure that regulate gene expression, which abundant in brain tissue. The abnormality of circRNAs may reflect the pathogenesis of TLE, but the roles of circRNAs in epilepsy are still limited. It has been found that circ-EFCAB2 and circ-DROSHA may be potential therapeutic targets and biomarkers for TLE patients(Li et al., 2018b).

Meanwhile, circ-DROSHA can regulate microRNA-106b-5p/MEF2C axis to reduce the neural damage in TLE cell model (Zheng et al., 2021). Circ-UBQLN1 upregulates microRNA-155-mediated SOX7, thereby inhibiting apoptosis and oxidative stress and promoting proliferation of hippocampal neurons in epilepsy(Zhu et al., 2021). Circ-ANKMY2 regulates the microRNA-106b-5p/FOXP1 axis to affect TLE progression (Lin et al., 2020). Circ-Hivep2 regulates microRNA-181a-5p/SOCS2 signaling to promote microglia activation and inflammation in KA-induced epileptic mice model (Xiaoying et al., 2020).

In a word, those results indicate the role for lncRNAs in modulating neuronal activity and suggest a novel mechanistic link between an activity-dependent lncRNA and epilepsy.

2.3.3N6-methyladenosine (m6A) modification.

As the most abundant epigenetic modification of eukaryotic mRNA, m6A methylation is considered to be the most common internal modification of mRNAs and ncRNAs in organisms(Tao et al., 2022; Yang et al., 2022). The occurrence of m6A methylation is controlled by a core methyltransferase complex, including methyltransferase-like 3 and 14 (METTL3 and METTL14) and wilms tumor 1-associated protein (WTAP)(You et al., 2022). Meanwhile, two m6A demethylases (FTO and ALKBH5) can specifically eliminate the m6A sites from target mRNAs(You et al., 2022). In addition, m6A-binding proteins mainly include YTH domain-containing RNA-binding proteins(YTHDF1/2/3), which can specifically recognize and bind to m6A-modified mRNA(Lei and Wang, 2022). Changes of m6A modification cause abnormal nervous system functions, including brain tissue development retardation, synaptic dysfunction, memory and cognitive function changes(Lei and Wang, 2022). It has been reported that m6A modification is highly enriched in the brain and plays an important role in CNS development and neurodegenerative diseases involved in Parkinson's disease (PD), Alzheimer's disease (AD), epilepsy(Livneh et al., 2020).

In knockout of METTL3 mice, the cerebellum is severely atrophied, and the weight of the whole brain and cerebellum is significantly reduced, and the decrease of m6A modification causes apoptosis in the cerebellum(Wang et al., 2018a). Deficient ALKBH5 can result in disturbance of the m6A modification of genes related to cerebellar development (Ma et al., 2018). The dysregulation of m6A modification impairs synapse formation and function. Knockdown of FTO in axons increases m6A modification of Growth associated protein 43 (GAP-43) mRNA, thereby reducing translation of GAP-43 mRNA and inhibiting axons(Yu et al., 2018). Meanwhile, some experiments have shown that the loss of YTHDF1 or YTHDF3 leads to synaptic dysfunction(Merkurjev et al., 2018). Those findings suggest that m6A modification is closely related to brain tissue development. METTL3-mediated m6A mRNA modification enhances learning and memory ability(Zhang et al., 2018d). Absent YTHDF1 in the hippocampus of adult mice, can lead to learning and memory deficits, and re-expression of YTHDF1 can repair the associated damage(Shi et al., 2018). Meanwhile, FTO is expressed in the CA1 region of the hippocampus of mice and negative feedback regulates the formation of memory(Walters et al., 2017). In addition, METTL3-mediated m6A modification facilitated processing and maturation of pri-microRNA-221 to upregulate microRNA-221-3p, thereby aggravating cognitive deficits of rats(Niu et al., 2022). Those studies suggest relationship between m6A modification and the formation of memory and cognitive. In human AD samples, it has been observed that a high concentration of METTL3 in insoluble fractions is correlated positively with the concentration of the insoluble tau protein(Huang et al., 2020). Meanwhile, FTO also promote the occurrence of AD by targeting TSC1-mTOR-Tau signaling(Li et al., 2018a). In epilepsy, epileptogenesis is closely related to NMDARs. However, overexpressed FTO in dopaminergic neurons reduces the level of mRNA m6A modification, induces the expression of NMDAR1, promotes oxidative stress and Ca^{2+} influx, thus promoting degeneration or apoptosis of neurons(Li et al., 2018a). Meanwhile, VPA can also induce the expression of FTO and FTO knockdown eliminated the inhibitory effect of VPA on MBD2 and Na1.3 expression in epilepsy(Tan et al., 2017). In addition, based on the evidence that microRNA-134 and microRNA-146a are involved in the pathogenesis of epilepsy, both microRNA-134 and microRNA-146a contain a potential m6A site in the seed region, which is thought to play an important role in microRNA recognition of target mRNA(Rowles et al., 2012). Those studies may suggest close relationship between m6A modification and epilepsy. However, there's not a lot of research about m6A modification in epilepsy. In a word, the study of m6A modification will be conducive

to reveal the underlying pathophysiological mechanism of neuropsychiatric diseases. Meanwhile, regulation of the level of m6A modification in the brain is an effective strategy for the treatment of CNS diseases, including epilepsy and decline of epilepsy-related cognitive and memory.

3. REST

NRSF, also known as REST, is a zinc finger transcription factor that is widely expressed in neuronal and non-neuronal cells(Soga et al., 2021; Su et al., 2022a). NRSF, a master regulator of the CNS, is the basis of neuronal differentiation, plasticity and survival, which is also involved in hyperexcitability, oxidative stress and neurodegeneration(Ghosh et al., 2021; Su et al., 2022a). REST is expressed in a wide range of brain regions, including the cerebral cortex and the hippocampus(Butler-Ryan and Wood, 2021). Relevant studies have found that the expression of REST is continuously upregulated in patients and animal models of epilepsy, so it has become the focus of epilepsy research(Butler-Ryan and Wood, 2021).

After binding to DNA, NRSF can bind to the neuron-restrictive silencer element (NRSE) to recruit co-repressors and then suppress transcription of NRSE downstream genes by epigenetic mechanisms(Su et al., 2022a). The N-terminal domain of NRSF can recruit the corepressor mSin3 by its paired amphipathic helix (PAH1) domain. mSin3 can recruit HDACs to nucleosomes, thereby promoting a chromatin repressive environment by histone deacetylation(Laherty et al., 1997; Nomura et al., 2005). Separately, the C-terminal domain can recruit REST corepressor 1 (CoREST), thereby recruiting chromatin modifying enzymes, including HDACs and HMT(Andrés et al., 1999; Yang et al., 2006). Meanwhile, CoREST contains two SANT domains that allow it to interact with histones(Yang et al., 2006). Finally, NRSF expression can be downregulated post-translationally by B-TrCP ubiquitination(Westbrook et al., 2008). In addition, REST-interacting LIM domain protein (RILP) is one of the chief nuclear importers of NRSF. The REST/NRSF plays an important role in nuclear translocation. RILP has been found to interact directly with ZFD5 of NRSF and is required for proper differentiation and maintenance of neuronal phenotypes(Shimojo and Hersh, 2006).

REST4, RILP, and CoREST play important roles in the regulation of NRSF activity. However, chromatin modifiers that leave repressive covalent modifications on histones and DNA can regulate the repressive function of NRSF(Thompson and Chan, 2018). Meanwhile, function of NRSF depends on recruitment of HDACs, HMT and DNA methylases, and NRSF also recruits mSin3a to its N-terminal region(Huang et al., 1999; Thompson and Chan, 2018). From there, mSin3a recruits HDACs that are essential for gene repression(Laherty et al., 1997). In addition, NRSF recruits G9a which appears to preferentially demethylate H3K9, and its activity does not overlap with HDAC repression from either mSin3a or CoREST(Roopra et al., 2004; Mulligan et al., 2008). Meanwhile, Chromodomain on Y-like (CDYL) bridges REST and HMT for gene repression and inhibition of cellular transformation(Mulligan et al., 2008). CoREST is seen as a recruiter for HDACs. In addition, CoREST can interact with methyl CpG binding protein 2 (MeCP2) or binds to methylated DNA to regulate long-term gene inhibition(Lunyak et al., 2002; Thompson and Chan, 2018).

In multiple models of epilepsy, the levels of REST mRNA and protein are consistently upregulated following seizures. In epilepsy patients, the levels of REST mRNA and protein are also overexpressed which correlates with the frequency of seizures(Navarrete-Modesto et al., 2019). In KA-induced seizures, the levels of REST mRNA and protein are increased in rat hippocampal and cortical neurons in vivo, with a downregulation of REST target genes, and REST protein peaks at 24 h after KA injection (Spencer et al., 2006; McClelland et al., 2011; Brennan et al., 2016; Carminati et al., 2019). In pilocarpine-induced epilepsy, the levels of REST mRNA and protein are upregulated 24 h after pilocarpine injection(Hu et al., 2011). Interestingly, REST protein expression is increased in PTZ-induced epilepsy and is resistant to kindling seizure(Chmielewska et al., 2020). Related studies have been found that REST can downregulate BDNF and TrkB to reduce excitability of neurons and protect against seizures, thereby playing a neuroprotective effect in the epilepsy brain(Butler-Ryan and Wood, 2021). Increased REST can also downregulate AMPAR subunit GluR2 and increase Ca^{2+} permeability, ultimately resulting in excitotoxicity, cell death and seizures(Butler-Ryan and Wood, 2021). In addition, REST, as an important regulator of epilepsy, can inhibit the expression of key neuronal genes KCC2 and GRIN2A(McClelland et al., 2011; McClelland et al., 2014). Those findings highlight

an association between REST increase and protection against seizures.

Epileptic encephalopathies (EE) are severe epilepsy syndromes characterized by multiple seizure types, developmental delay and even regression. Increasingly, it is believed to be caused by de novo genetic mutations, including many identified mutations in chromodomain helicase DNA binding (CHD) protein family(Wilson et al., 2021). Related studies have been demonstrated that CHD2 directly binds to REST gene, and REST expression is decreased when CHD2 is silenced. REST-mediated neural differentiation is facilitated by CHD2 expression, which occurs by a direct association between the REST gene and CHD2 protein, rather than H3K4me-mediated processes(Shen et al., 2015). However, the interaction between CHD2 and NRSF in this context has yet to be investigated. In addition, some microRNAs such as microRNA-9, microRNA-124a, and microRNA-132 have been identified to target REST with direct roles in epigenetics(Wu and Xie, 2006). Related studies have found that the functional and structural effects of NRSF can regulate persistent memory impairment caused by developmental febrile epilepsy(Patterson et al., 2017). In progressive myoclonus epilepsy-ataxia syndrome, RILP mutations result in mislocalization of NRSF, thereby preventing the binding of RILP to NRSF and cause the accumulation of NRSF in the nucleus(Bassuk et al., 2008). NRSF and REST4 expression are increased during seizures with upregulated proconvulsant gene *TAC3* (Gillies et al., 2009). It was found that increased REST4 expression may regulate NRSF to competitively inhibit the repression of NKB (Thompson and Chan, 2018). Abnormal regulation of potassium voltage-gated channel subfamily Q member 2 (KCNQ2), KCNQ3 and the ion channel genes SCN2A promotes the progression of infant epilepsy, and these genes are inhibited by NRSF(Mucha et al., 2010). In addition, NRSF regulates hyperpolarization-activated cyclic adenosine monophosphate gated channel type 1 (HCN1) channelopathy in TLE(McClelland et al., 2011). The dysregulation of NRSF seems to be implicated in epilepsy, and specific mechanisms are still lacking. Those findings highlight therapeutic potential of REST modulation through gene therapy in epilepsy patients.

4. Conclusions

In this review, we reviewed that epigenetic regulation, such as histone modifications, DNA methylation, ncRNAs and REST/NRSF in epilepsy. Increasing evidence suggests that epigenetic mechanisms play a functional role in epileptogenesis and therapeutic reconstruction of the epigenome is an effective antiepileptogenic therapy. In addition, some drugs may also play an antiepileptic role through epigenetic mechanisms. Studying the role of various epigenetic mechanisms in epilepsy may be beneficial to understand the epileptogenesis and therapy of epilepsy. At present, there are many ways of epigenetic regulation, but the mechanisms of epigenetic regulation in epileptogenesis and therapy of epilepsy is not fully understood. Therefore, targeting epigenetic regulation may be a new approach to suppress seizures and the progression of epilepsy, which is yet to be discovered and explored.

Author Contributions

SC and DX searched the references and participated in drafting the manuscript. ML designed research plans, provided research direction, supervised the work and modified the final manuscript.

Conflict of Interest

The authors declared no potential conflict of interest.

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References

Almeida Silva, L., Reschke, C., Nguyen, N., Langa, E., Sanz-Rodriguez, A., Gerbatin, R., et al. (2020). Genetic deletion of microRNA-22 blunts the inflammatory transcriptional response to status epilepticus and exacerbates epilepsy in mice. *Molecular brain* 13(1)**,**114. doi: 10.1186/s13041-020-00653-x.

Alsharafi, W., and Xiao, B. (2015). Dynamic Expression of MicroRNAs (183, 135a, 125b, 128, 30c and 27a) in the Rat Pilocarpine Model and Temporal Lobe Epilepsy Patients. *CNS & neurological disorders drug targets* 14(8), 1096-1102. doi: 10.2174/1871527314666150317225945.

Alsharafi, W., Xiao, B., and Li, J. (2016). MicroRNA-139-5p negatively regulates NR2A-containing NMDA receptor in the rat pilocarpine model and patients with temporal lobe epilepsy. *Epilepsia* 57(11),1931-1940. doi: 10.1111/epi.13568.

Andrés, M., Burger, C., Peral-Rubio, M., Battaglioli, E., Anderson, M., Grimes, J., et al. (1999). CoREST: a functional corepressor required for regulation of neural-specific gene expression. *Proceedings of the National Academy of Sciences of the United States of America*96(17), 9873-9878. doi: 10.1073/pnas.96.17.9873.

Aronica, E., Fluiter, K., Iyer, A., Zurolo, E., Vreijling, J., van Vliet, E., et al. (2010). Expression pattern of miR-146a, an inflammation-associated microRNA, in experimental and human temporal lobe epilepsy. *The European journal of neuroscience*31(6), 1100-1107. doi: 10.1111/j.1460-9568.2010.07122.x.

Barry, G., Briggs, J., Hwang, D., Nayler, S., Fortuna, P., Jonkhout, N., et al. (2017). The long non-coding RNA NEAT1 is responsive to neuronal activity and is associated with hyperexcitability states.*Scientific reports* 7, 40127. doi: 10.1038/srep40127.

Bassuk, A., Wallace, R., Buhr, A., Buller, A., Afawi, Z., Shimojo, M., et al. (2008). A homozygous mutation in human PRICKLE1 causes an autosomal-recessive progressive myoclonus epilepsy-ataxia syndrome.*American journal of human genetics* 83(5), 572-581. doi: 10.1016/j.ajhg.2008.10.003.

Basu, T., O'Riordan, K., Schoenike, B., Khan, N., Wallace, E., Rodriguez, G., et al. (2019). Histone deacetylase inhibitors restore normal hippocampal synaptic plasticity and seizure threshold in a mouse model of Tuberous Sclerosis Complex. *Scientific reports*9(1), 5266. doi: 10.1038/s41598-019-41744-7.

Bayraktar, G., Yuanxiang, P., Confettura, A., Gomes, G., Raza, S., Stork, O., et al. (2020). Synaptic control of DNA methylation involves activity-dependent degradation of DNMT3A1 in the nucleus.*Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 45(12), 2120-2130. doi: 10.1038/s41386-020-0780-2.

Beamer, E., Jurado-Arjona, J., Jimenez-Mateos, E., Morgan, J., Reschke, C., Kenny, A., et al. (2018). MicroRNA-22 Controls Aberrant Neurogenesis and Changes in Neuronal Morphology After Status Epilepticus.*Frontiers in molecular neuroscience* 11, 442. doi: 10.3389/fnmol.2018.00442.

Bekenstein, U., Mishra, N., Milikovsky, D., Hanin, G., Zelig, D., Sheintuch, L., et al. (2017). Dynamic changes in murine forebrain miR-211 expression associate with cholinergic imbalances and epileptiform activity. *Proceedings of the National Academy of Sciences of the United States of America* 114(25), E4996-E5005. doi: 10.1073/pnas.1701201114.

Berger, T., Vigeland, M., Hjorthaug, H., Nome, C., Taubøll, E., Selmer, K., et al. (2020). Differential Glial Activation in Early Epileptogenesis-Insights From Cell-Specific Analysis of DNA Methylation and Gene Expression in the Contralateral Hippocampus. *Frontiers in neurology* 11, 573575. doi: 10.3389/fneur.2020.573575.

Blaauboer, A., van Koetsveld, P., Mustafa, D., Dumas, J., Dogan, F., van Zwienen, S., et al. (2022). The Class I HDAC Inhibitor Valproic Acid Strongly Potentiates Gemcitabine Efficacy in Pancreatic Cancer by Immune System Activation. *Biomedicines* 10(3). doi: 10.3390/biomedicines10030517.

Boison, D., and Rho, J. (2020). Epigenetics and epilepsy prevention: The therapeutic potential of adenosine and metabolic therapies.*Neuropharmacology* 167, 107741. doi: 10.1016/j.neuropharm.2019.107741.

Boyault, C., Sadoul, K., Pabion, M., and Khochbin, S. (2007). HDAC6, at the crossroads between cytoskeleton and cell signaling by acetylation and ubiquitination. *Oncogene* 26(37), 5468-5476. doi: 10.1038/sj.onc.1210614.

Brennan, G., Dey, D., Chen, Y., Patterson, K., Magnetta, E., Hall, A., et al. (2016). Dual and Opposing Roles of MicroRNA-124 in Epilepsy Are Mediated through Inflammatory and NRSF-Dependent Gene Networks.*Cell reports* 14(10)**,** 2402-2412. doi: 10.1016/j.celrep.2016.02.042.

Broekaart, D., van Scheppingen, J., Anink, J., Wierts, L., van Het Hof, B., Jansen, F., et al. (2020). Increased matrix metalloproteinases expression in tuberous sclerosis complex: modulation by microRNA 146a and 147b in vitro. *Neuropathology and applied neurobiology*46(2)**,** 142-159. doi: 10.1111/nan.12572.

Butler-Ryan, R., and Wood, I. (2021). The functions of repressor element 1-silencing transcription factor in models of epileptogenesis and post-ischemia. *Metabolic brain disease* 36(6)**,** 1135-1150. doi: 10.1007/s11011-021-00719-2.

Cai, X., Long, L., Zeng, C., Ni, G., Meng, Y., Guo, Q., et al. (2020). LncRNA ILF3-AS1 mediated the occurrence of epilepsy through suppressing hippocampal miR-212 expression. *Aging* 12(9)**,** 8413-8422. doi: 10.18632/aging.103148.

Cai, Z., Li, S., Li, S., Song, F., Zhang, Z., Qi, G., et al. (2016). Antagonist Targeting microRNA-155 Protects against Lithium-Pilocarpine-Induced Status Epilepticus in C57BL/6 Mice by Activating Brain-Derived Neurotrophic Factor. *Frontiers in pharmacology* 7**,** 129. doi: 10.3389/fphar.2016.00129.

Caramaschi, D., Hatcher, C., Mulder, R., Felix, J., Cecil, C., Relton, C., et al. (2020). Epigenome-wide association study of seizures in childhood and adolescence. *Clinical epigenetics* 12(1)**,**8. doi: 10.1186/s13148-019-0793-z.

Carminati, E., Buffolo, F., Rocchi, A., Michetti, C., Cesca, F., and Benfenati, F. (2019). Mild Inactivation of RE-1 Silencing Transcription Factor (REST) Reduces Susceptibility to Kainic Acid-Induced Seizures.*Frontiers in cellular neuroscience* 13**,** 580. doi: 10.3389/fncel.2019.00580.

Cattani, A., Allene, C., Seifert, V., Rosenow, F., Henshall, D., and Freiman, T. (2016). Involvement of microRNAs in epileptogenesis.*Epilepsia* 57(7)**,** 1015-1026. doi: 10.1111/epi.13404.

Chen, D., Wang, W., Chen, Y., Yang, X., Zhao, M., and Yang, Y. (2019). miR-128 is upregulated in epilepsy and promotes apoptosis through the SIRT1 cascade. *International journal of molecular medicine*44(2)**,** 694-704. doi: 10.3892/ijmm.2019.4223.

Chen, M., Lai, X., Wang, X., Ying, J., Zhang, L., Zhou, B., et al. (2021a). Long Non-coding RNAs and Circular RNAs: Insights Into Microglia and Astrocyte Mediated Neurological Diseases. *Frontiers in molecular neuroscience* 14**,** 745066. doi: 10.3389/fnmol.2021.745066.

Chen, S., Chen, Y., Zhang, Y., Kuang, X., Liu, Y., Guo, M., et al. (2020). Iron Metabolism and Ferroptosis in Epilepsy. *Frontiers in neuroscience* 14**,** 601193. doi: 10.3389/fnins.2020.601193.

Chen, S., Xu, D., Fan, L., Fang, Z., Wang, X., and Li, M. (2021b). Roles of N-Methyl-D-Aspartate Receptors (NMDARs) in Epilepsy. *Frontiers in molecular neuroscience* 14**,** 797253. doi: 10.3389/fnmol.2021.797253.

Chen, S., Ye, J., Chen, X., Shi, J., Wu, W., Lin, W., et al. (2018). Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-κB pathway dependent of HDAC3.*Journal of neuroinflammation* 15(1)**,** 150. doi: 10.1186/s12974-018-1193-6.

Chen, X., Peng, X., Wang, L., Fu, X., Zhou, J., Zhu, B., et al. (2017). Association of RASgrf1 methylation with epileptic seizures.*Oncotarget* 8(28)**,** 46286-46297. doi: 10.18632/oncotarget.18000.

Chmielewska, N., Wawer, A., Maciejak, P., Turzyńska, D., Sobolewska, A., Skórzewska, A., et al. (2020). The role of REST/NRSF, TrkB and BDNF in neurobiological mechanisms of different susceptibility to seizure in a PTZ model of epilepsy. *Brain research bulletin* 158**,**108-115. doi: 10.1016/j.brainresbull.2020.03.007.

Citraro, R., Leo, A., De Caro, C., Nesci, V., Gallo Cantafio, M., Amodio, N., et al. (2020). Effects of Histone Deacetylase Inhibitors on the Development of Epilepsy and Psychiatric Comorbidity in WAG/Rij Rats.*Molecular neurobiology* 57(1)**,** 408-421. doi: 10.1007/s12035-019-01712-8.

Citraro, R., Leo, A., Santoro, M., D'agostino, G., Constanti, A., and Russo, E. (2017). Role of Histone Deacetylases (HDACs) in Epilepsy and Epileptogenesis. *Current pharmaceutical design* 23(37),5546-5562. doi: 10.2174/1381612823666171024130001.

Cui, H., and Zhang, W. (2022). βThe Neuroprotective Effect of miR-136 on Pilocarpine-Induced Temporal Lobe Epilepsy Rats by Inhibiting Wnt/-Catenin Signaling Pathway. *Computational and mathematical methods in medicine* 2022, 1938205. doi: 10.1155/2022/1938205.

D'Aiuto, L., Di Maio, R., Mohan, K., Minervini, C., Saporiti, F., Soreca, I., et al. (2011). Mouse ES cells overexpressing DNMT1 produce abnormal neurons with upregulated NMDA/NR1 subunit.*Differentiation; research in biological diversity* 82(1),9-17. doi: 10.1016/j.diff.2011.03.003.

d'Ydewalle, C., Bogaert, E., and Van Den Bosch, L. (2012). HDAC6 at the Intersection of Neuroprotection and Neurodegeneration. *Traffic (Copenhagen, Denmark)* 13(6), 771-779. doi: 10.1111/j.1600-0854.2012.01347.x.

Dash, P., Orsi, S., and Moore, A. (2009). Histone deactylase inhibition combined with behavioral therapy enhances learning and memory following traumatic brain injury. *Neuroscience* 163(1), 1-8. doi: 10.1016/j.neuroscience.2009.06.028.

De Benedittis, S., Fortunato, F., Cava, C., Gallivanone, F., Iaccino, E., Caligiuri, M., et al. (2021). Circulating microRNA: The Potential Novel Diagnostic Biomarkers to Predict Drug Resistance in Temporal Lobe Epilepsy, a Pilot Study. *International journal of molecular sciences* 22(2). doi: 10.3390/ijms22020702.

de Nijs, L., Choe, K., Steinbusch, H., Schijns, O., Dings, J., van den Hove, D., et al. (2019). DNA methyltransferase isoforms expression in the temporal lobe of epilepsy patients with a history of febrile seizures. *Clinical epigenetics* 11(1), 118. doi: 10.1186/s13148-019-0721-2.

de Sousa Maciel, I., Sales, A., Casarotto, P., Castrén, E., Biojone, C., and Joca, S. (2020). Nitric Oxide Synthase inhibition counteracts the stress-induced DNA methyltransferase 3b expression in the hippocampus of rats. *The European journal of neuroscience* . doi: 10.1111/ejn.15042.

Debski, K., Pitkanen, A., Puhakka, N., Bot, A., Khurana, I., Harikrishnan, K., et al. (2016). Etiology matters - Genomic DNA Methylation Patterns in Three Rat Models of Acquired Epilepsy.*Scientific reports* 6, 25668. doi: 10.1038/srep25668.

Dedoni, S., Marras, L., Olianas, M., Ingianni, A., and Onali, P. (2019). Downregulation of TrkB Expression and Signaling by Valproic Acid and Other Histone Deacetylase Inhibitors. *The Journal of pharmacology and experimental therapeutics* 370(3), 490-503. doi: 10.1124/jpet.119.258129.

Deutsch, S., Mastropaolo, J., Burket, J., and Rosse, R. (2009). An epigenetic intervention interacts with genetic strain differences to modulate the stress-induced reduction of flurazepam's antiseizure efficacy in the mouse. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*19(6), 398-401. doi: 10.1016/j.euroneuro.2008.12.011.

Deutsch, S., Rosse, R., Long, K., Gaskins, B., Burket, J., and Mastropaolo, J. (2008). Sodium butyrate, an epigenetic interventional strategy, attenuates a stress-induced alteration of MK-801's pharmacologic action. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*18(8), 565-568. doi: 10.1016/j.euroneuro.2007.11.004.

Diao, L., Yu, H., Li, H., Hu, Y., Li, M., He, Q., et al. (2021). LncRNA UCA1 alleviates aberrant hippocampal neurogenesis through regulating miR-375/SFRP1-mediated WNT/β-catenin pathway in kainic acid-induced epilepsy. *Acta biochimica Polonica* 68(2), 159-167. doi: 10.18388/abp.2020_5448.

Dixit, A., Sharma, D., Tripathi, M., Srivastava, A., Paul, D., Prakash, D., et al. (2018). Genome-wide DNA Methylation and RNAseq Analyses Identify Aberrant Signalling Pathways in Focal Cortical Dysplasia (FCD) Type II. *Scientific reports* 8(1), 17976. doi: 10.1038/s41598-018-35892-5.

Du, Y., Chi, X., and An, W. (2019). Downregulation of microRNA-200c-3p reduces damage of hippocampal neurons in epileptic rats by upregulating expression of RECK and inactivating the AKT signaling pathway.*Chemico-biological interactions* 307**,** 223-233. doi: 10.1016/j.cbi.2019.04.027.

Duan, W., Chen, Y., and Wang, X. (2018). MicroRNA-155 contributes to the occurrence of epilepsy through the PI3K/Akt/mTOR signaling pathway.*International journal of molecular medicine* 42(3)**,**1577-1584. doi: 10.3892/ijmm.2018.3711.

Fachim, H., Loureiro, C., Corsi-Zuelli, F., Shuhama, R., Louzada-Junior, P., Menezes, P., et al. (2019). GRIN2B promoter methylation deficits in early-onset schizophrenia and its association with cognitive function.*Epigenomics* 11(4)**,** 401-410. doi: 10.2217/epi-2018-0127.

Fan, Y., Wang, W., Li, W., and Li, X. (2020). miR-15a inhibits cell apoptosis and inflammation in a temporal lobe epilepsy model by downregulating GFAP. *Molecular medicine reports* 22(4)**,**3504-3512. doi: 10.3892/mmr.2020.11388.

Feng, H., Gui, Q., Wu, G., Zhu, W., Dong, X., Shen, M., et al. (2021). Long noncoding RNA Nespas inhibits apoptosis of epileptiform hippocampal neurons by inhibiting the PI3K/Akt/mTOR pathway. *Experimental cell research* 398(1)**,** 112384. doi: 10.1016/j.yexcr.2020.112384.

Feng, X., Xiong, W., Yuan, M., Zhan, J., Zhu, X., Wei, Z., et al. (2019). Down-regulated microRNA-183 mediates the Jak/Stat signaling pathway to attenuate hippocampal neuron injury in epilepsy rats by targeting Foxp1. *Cell cycle (Georgetown, Tex.)* 18(22)**,**3206-3222. doi: 10.1080/15384101.2019.1671717.

Feng, Y., Duan, C., Luo, Z., Xiao, W., and Tian, F. (2020). Silencing miR-20a-5p inhibits axonal growth and neuronal branching and prevents epileptogenesis through RGMa-RhoA-mediated synaptic plasticity.*Journal of cellular and molecular medicine* 24(18)**,**10573-10588. doi: 10.1111/jcmm.15677.

Fernandes, J., Acuña, S., Aoki, J., Floeter-Winter, L., and Muxel, S. (2019). Long Non-Coding RNAs in the Regulation of Gene Expression: Physiology and Disease. *Non-coding RNA* 5(1). doi: 10.3390/ncrna5010017.

Fonseca-Barriendos, D., Frías-Soria, C., Pérez-Pérez, D., Gómez-López, R., Borroto Escuela, D., and Rocha, L. (2021). Drug-Resistant Epilepsy: drug target hypothesis and beyond the receptors. *Epilepsia open* . doi: 10.1002/epi4.12539.

Fu, H., Cheng, Y., Luo, H., Rong, Z., Li, Y., Lu, P., et al. (2019). Silencing MicroRNA-155 Attenuates Kainic Acid-Induced Seizure by Inhibiting Microglia Activation. *Neuroimmunomodulation*26(2)**,** 67-76. doi: 10.1159/000496344.

Fu, M., Tao, J., Wang, D., Zhang, Z., Wang, X., Ji, Y., et al. (2020). Downregulation of MicroRNA-34c-5p facilitated neuroinflammation in drug-resistant epilepsy. *Brain research* 1749**,** 147130. doi: 10.1016/j.brainres.2020.147130.

Fu, M., Zhu, Y., Zhang, J., Wu, W., Sun, Y., Zhang, X., et al. (2021). MicroRNA-221-3p Suppresses the Microglia Activation and Seizures by Inhibiting of HIF-1α in Valproic Acid-Resistant Epilepsy.*Frontiers in pharmacology* 12**,** 714556. doi: 10.3389/fphar.2021.714556.

Gan, J., Qu, Y., Li, J., Zhao, F., and Mu, D. (2015). An evaluation of the links between microRNA, autophagy, and epilepsy. *Reviews in the neurosciences* 26(2)**,** 225-237. doi: 10.1515/revneuro-2014-0062.

Gattás, D., Neto, F., Freitas-Lima, P., Bonfim-Silva, R., de Almeida, S., de Assis Cirino, M., et al. (2022). MicroRNAs miR-629-3p, miR-1202 and miR-1225-5p as potential diagnostic and surgery outcome biomarkers for mesial temporal lobe epilepsy with hippocampal sclerosis.*Neuro-Chirurgie* . doi: 10.1016/j.neuchi.2022.06.002.

Geng, J., Liu, X., Zhao, H., Fan, W., Geng, J., and Liu, X. (2018). LncRNA UCA1 inhibits epilepsy and seizure-induced brain injury by regulating miR-495/Nrf2-ARE signal pathway. *The international journal of biochemistry & cell biology* 99**,** 133-139. doi: 10.1016/j.biocel.2018.03.021.

Geng, J., Zhao, H., Liu, X., Geng, J., Gao, Y., and He, B. (2021). MiR-101a-3p Attenuated Pilocarpine-Induced Epilepsy by Downregulating c-FOS. *Neurochemical research* 46(5)**,** 1119-1128. doi: 10.1007/s11064-021-03245-w.

Ghiglieri, V., Sgobio, C., Patassini, S., Bagetta, V., Fejtova, A., Giampà, C., et al. (2010). TrkB/BDNF-dependent striatal plasticity and behavior in a genetic model of epilepsy: modulation by valproic acid.*Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 35(7)**,** 1531-1540. doi: 10.1038/npp.2010.23.

Ghosh, I., Liu, C., Swardfager, W., Lanctôt, K., and Anderson, N. (2021). The potential roles of excitatory-inhibitory imbalances and the repressor element-1 silencing transcription factor in aging and aging-associated diseases. *Molecular and cellular neurosciences*117**,** 103683. doi: 10.1016/j.mcn.2021.103683.

Gillies, S., Haddley, K., Vasiliou, S., Bubb, V., and Quinn, J. (2009). The human neurokinin B gene, TAC3, and its promoter are regulated by Neuron Restrictive Silencing Factor (NRSF) transcription factor family.*Neuropeptides* 43(4)**,** 333-340. doi: 10.1016/j.npep.2009.05.004.

Gregoretti, I., Lee, Y., and Goodson, H. (2004). Molecular evolution of the histone deacetylase family: functional implications of phylogenetic analysis. *Journal of molecular biology* 338(1)**,** 17-31. doi: 10.1016/j.jmb.2004.02.006.

Haenisch, S., von Rüden, E., Wahmkow, H., Rettenbeck, M., Michler, C., Russmann, V., et al. (2016). miRNA-187-3p-Mediated Regulation of the KCNK10/TREK-2 Potassium Channel in a Rat Epilepsy Model. *ACS chemical neuroscience* 7(11)**,** 1585-1594. doi: 10.1021/acschemneuro.6b00222.

Hamamoto, O., Tirapelli, D., Lizarte Neto, F., Freitas-Lima, P., Saggioro, F., Cirino, M., et al. (2020). Modulation of NMDA receptor by miR-219 in the amygdala and hippocampus of patients with mesial temporal lobe epilepsy. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 74**,** 180-186. doi: 10.1016/j.jocn.2020.02.024.

Han, C., Ge, M., Liu, Y., Zhao, X., Wang, K., Chen, N., et al. (2018a). Long non-coding RNA H19 contributes to apoptosis of hippocampal neurons by inhibiting let-7b in a rat model of temporal lobe epilepsy.*Cell death & disease* 9(6)**,** 617. doi: 10.1038/s41419-018-0496-y.

Han, C., Ge, M., Liu, Y., Zhao, X., Wang, K., Chen, N., et al. (2018b). LncRNA H19 contributes to hippocampal glial cell activation via JAK/STAT signaling in a rat model of temporal lobe epilepsy. *Journal of neuroinflammation* 15(1)**,** 103. doi: 10.1186/s12974-018-1139-z.

Han, D., Huang, M., Wang, T., Li, Z., Chen, Y., Liu, C., et al. (2019). Lysine methylation of transcription factors in cancer. *Cell death & disease* 10(4)**,** 290. doi: 10.1038/s41419-019-1524-2.

Hauser, R., Henshall, D., and Lubin, F. (2018). The Epigenetics of Epilepsy and Its Progression. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry* 24(2)**,**186-200. doi: 10.1177/1073858417705840.

He, C., Su, C., Zhang, W., Zhou, Q., Shen, X., Yang, J., et al. (2021a). Modulatory Potential of LncRNA Zfas1 for Inflammation and Neuronal Apoptosis in Temporal Lobe Epilepsy. *Yonsei medical journal*62(3)**,** 215-223. doi: 10.3349/ymj.2021.62.3.215.

He, Z., Chen, H., Zhong, Y., Yang, Q., Wang, X., Chen, R., et al. (2021b). MicroRNA 223 Targeting ATG16L1 Affects Microglial Autophagy in the Kainic Acid Model of Temporal Lobe Epilepsy. *Frontiers in neurology* 12**,** 704550. doi: 10.3389/fneur.2021.704550.

Heikkinen, A., Bollepalli, S., and Ollikainen, M. (2022). The potential of DNA methylation as a biomarker for obesity and smoking. *Journal of internal medicine* . doi: 10.1111/joim.13496.

Henshall, D. (2018). Epigenetic changes in status epilepticus.*Epilepsia* **,** 82-86. doi: 10.1111/epi.14502.

Henshall, D., and Kobow, K. (2015). Epigenetics and Epilepsy. *Cold Spring Harbor perspectives in medicine* 5(12). doi: 10.1101/cshperspect.a022731.

Hiraide, T., Nakashima, M., Yamoto, K., Fukuda, T., Kato, M., Ikeda, H., et al. (2018). De novo variants in SETD1B are associated with intellectual disability, epilepsy and autism. *Human genetics*137(1), 95-104. doi: 10.1007/s00439-017-1863-y.

Hon, G., Hawkins, R., and Ren, B. (2009). Predictive chromatin signatures in the mammalian genome. *Human molecular genetics*18, R195-201. doi: 10.1093/hmg/ddp409.

Hu, F., Shao, L., Zhang, J., Zhang, H., Wen, A., and Zhang, P. (2020a). Knockdown of ZFAS1 Inhibits Hippocampal Neurons Apoptosis and Autophagy by Activating the PI3K/AKT Pathway via Up-regulating miR-421 in Epilepsy. *Neurochemical research* 45(10), 2433-2441. doi: 10.1007/s11064-020-03103-1.

Hu, G., Niu, F., Humburg, B., Liao, K., Bendi, S., Callen, S., et al. (2018). Molecular mechanisms of long noncoding RNAs and their role in disease pathogenesis. *Oncotarget* 9(26), 18648-18663. doi: 10.18632/oncotarget.24307.

Hu, T., Chung, H., Ping, L., Hsu, S., Tsai, H., Chen, S., et al. (2020b). Differential Expression of Multiple Disease-Related Protein Groups Induced by Valproic Acid in Human SH-SY5Y Neuroblastoma Cells.*Brain sciences* 10(8). doi: 10.3390/brainsci10080545.

Hu, X., Cheng, X., Cai, L., Tan, G., Xu, L., Feng, X., et al. (2011). Conditional deletion of NRSF in forebrain neurons accelerates epileptogenesis in the kindling model. *Cerebral cortex (New York, N.Y. : 1991)* 21(9), 2158-2165. doi: 10.1093/cercor/bhq284.

Huang, G., Chen, J., Zhou, J., Xiao, S., Zeng, W., Xia, J., et al. (2021). Epigenetic modification and BRAF gene mutation in thyroid carcinoma. *Cancer cell international* 21(1), 687. doi: 10.1186/s12935-021-02405-w.

Huang, H., Camats-Perna, J., Medeiros, R., Anggono, V., and Widagdo, J. (2020). Altered Expression of the m6A Methyltransferase METTL3 in Alzheimer's Disease. *eNeuro* 7(5). doi: 10.1523/eneuro.0125-20.2020.

Huang, Y., Doherty, J., and Dingledine, R. (2002). Altered histone acetylation at glutamate receptor 2 and brain-derived neurotrophic factor genes is an early event triggered by status epilepticus. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 22(19), 8422-8428. doi: 10.1523/jneurosci.22-19-08422.2002.

Huang, Y., Liu, X., Liao, Y., Liao, Y., Zou, D., Wei, X., et al. (2018). Role of miR-34c in the cognitive function of epileptic rats induced by pentylenetetrazol. *Molecular medicine reports* 17(3),4173-4180. doi: 10.3892/mmr.2018.8441.

Huang, Y., Myers, S., and Dingledine, R. (1999). Transcriptional repression by REST: recruitment of Sin3A and histone deacetylase to neuronal genes. *Nature neuroscience* 2(10), 867-872. doi: 10.1038/13165.

Irwin, A., Bahabry, R., and Lubin, F. (2021). A putative role for lncRNAs in epigenetic regulation of memory. *Neurochemistry international* , 105184. doi: 10.1016/j.neuint.2021.105184.

Jang, Y., Moon, J., Lee, S., Jun, J., Kim, T., Lim, J., et al. (2018). Dysregulated long non-coding RNAs in the temporal lobe epilepsy mouse model. *Seizure* 58, 110-119. doi: 10.1016/j.seizure.2018.04.010.

Jiang, Y., Jakovcevski, M., Bharadwaj, R., Connor, C., Schroeder, F., Lin, C., et al. (2010). Setdb1 histone methyltransferase regulates mood-related behaviors and expression of the NMDA receptor subunit NR2B. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 30(21), 7152-7167. doi: 10.1523/jneurosci.1314-10.2010.

Jimenez-Mateos, E., Arribas-Blazquez, M., Sanz-Rodriguez, A., Concannon, C., Olivos-Ore, L., Reschke, C., et al. (2015). microRNA targeting of the P2X7 purinoceptor opposes a contralateral epileptogenic focus in the hippocampus. *Scientific reports* 5, 17486. doi: 10.1038/srep17486.

Jimenez-Mateos, E., Bray, I., Sanz-Rodriguez, A., Engel, T., McKiernan, R., Mouri, G., et al. (2011). miRNA Expression profile after status epilepticus and hippocampal neuroprotection by targeting miR-132. *The American journal of pathology* 179(5), 2519-2532. doi: 10.1016/j.ajpath.2011.07.036.

Jimenez-Mateos, E., Engel, T., Merino-Serrais, P., McKiernan, R., Tanaka, K., Mouri, G., et al. (2012). Silencing microRNA-134 produces neuroprotective and prolonged seizure-suppressive effects. *Nature medicine* 18(7), 1087-1094. doi: 10.1038/nm.2834.

Jin, Y., Liu, T., Luo, H., Liu, Y., and Liu, D. (2022). Targeting Epigenetic Regulatory Enzymes for Cancer Therapeutics: Novel Small-Molecule Epidrug Development. *Frontiers in oncology*12, 848221. doi: 10.3389/fonc.2022.848221.

Kiese, K., Jablonski, J., Hackenbracht, J., Wrosch, J., Groemer, T., Kornhuber, J., et al. (2017). Epigenetic control of epilepsy target genes contributes to a cellular memory of epileptogenesis in cultured rat hippocampal neurons. *Acta neuropathologica communications*5(1), 79. doi: 10.1186/s40478-017-0485-x.

Kobow, K., Ziemann, M., Kaipananickal, H., Khurana, I., Mühlebner, A., Feucht, M., et al. (2019). Genomic DNA methylation distinguishes subtypes of human focal cortical dysplasia. *Epilepsia*60(6), 1091-1103. doi: 10.1111/epi.14934.

Kong, H., Wang, H., Zhuo, Z., Li, Z., Tian, P., Wu, J., et al. (2020). Inhibition of miR-181a-5p reduces astrocyte and microglia activation and oxidative stress by activating SIRT1 in immature rats with epilepsy. *Laboratory investigation; a journal of technical methods and pathology* 100(9), 1223-1237. doi: 10.1038/s41374-020-0444-1.

Korotkov, A., Broekaart, D., Banchaewa, L., Pustjens, B., van Scheppingen, J., Anink, J., et al. (2020). microRNA-132 is overexpressed in glia in temporal lobe epilepsy and reduces the expression of pro-epileptogenic factors in human cultured astrocytes. *Glia*68(1), 60-75. doi: 10.1002/glia.23700.

Korotkov, A., Broekaart, D., van Scheppingen, J., Anink, J., Baayen, J., Idema, S., et al. (2018). Increased expression of matrix metalloproteinase 3 can be attenuated by inhibition of microRNA-155 in cultured human astrocytes. *Journal of neuroinflammation*15(1), 211. doi: 10.1186/s12974-018-1245-y.

Korotkov, A., Sim, N., Luinenburg, M., Anink, J., van Scheppingen, J., Zimmer, T., et al. (2021). MicroRNA-34a activation in tuberous sclerosis complex during early brain development may lead to impaired corticogenesis. *Neuropathology and applied neurobiology*47(6), 796-811. doi: 10.1111/nan.12717.

Krzyzewska, I., Maas, S., Henneman, P., Lip, K., Venema, A., Baranano, K., et al. (2019). A genome-wide DNA methylation signature for SETD1B-related syndrome. *Clinical epigenetics* 11(1),156. doi: 10.1186/s13148-019-0749-3.

Labbé, R., Holowatyj, A., and Yang, Z. (2013). Histone lysine demethylase (KDM) subfamily 4: structures, functions and therapeutic potential. *American journal of translational research*6(1), 1-15.

Laherty, C., Yang, W., Sun, J., Davie, J., Seto, E., and Eisenman, R. (1997). Histone deacetylases associated with the mSin3 corepressor mediate mad transcriptional repression. *Cell* 89(3),349-356. doi: 10.1016/s0092-8674(00)80215-9.

Leduc, C., Chemin, G., Puget, N., Sawan, C., Moutahir, M., Herceg, Z., et al. (2014). Tissue-specific inactivation of HAT cofactor TRRAP reveals its essential role in B cells. *Cell cycle (Georgetown, Tex.)* 13(10), 1583-1589. doi: 10.4161/cc.28560.

Lee, D., Moon, J., Lee, S., Jung, K., Park, D., Yoo, J., et al. (2015). Dysregulation of long non-coding RNAs in mouse models of localization-related epilepsy. *Biochemical and biophysical research communications* 462(4), 433-440. doi: 10.1016/j.bbrc.2015.04.149.

Lee, S., Jeon, D., Chu, K., Jung, K., Moon, J., Sunwoo, J., et al. (2017). Inhibition of miR-203 Reduces

Spontaneous Recurrent Seizures in Mice. *Molecular neurobiology* 54(5), 3300-3308. doi: 10.1007/s12035-016-9901-7.

Lei, C., and Wang, Q. (2022). The Progression of N6-methyladenosine Study and Its Role in Neuropsychiatric Disorders. *International journal of molecular sciences* 23(11). doi: 10.3390/ijms23115922.

Li, B., Wu, W., Zheng, H., Yang, H., Zuo, Y., and Cui, X. (2019a). Long noncoding RNA GAS5 silencing inhibits the expression of KCNQ3 by sponging miR-135a-5p to prevent the progression of epilepsy. *The Kaohsiung journal of medical sciences* 35(9), 527-534. doi: 10.1002/kjm2.12102.

Li, C., Zheng, X., Liu, P., and Li, M. (2021). Clinical value of lncRNA TUG1 in temporal lobe epilepsy and its role in the proliferation of hippocampus neuron via sponging miR-199a-3p. *Bioengineered*12(2), 10666-10673. doi: 10.1080/21655979.2021.2001904.

Li, H., Ren, Y., Mao, K., Hua, F., Yang, Y., Wei, N., et al. (2018a). FTO is involved in Alzheimer's disease by targeting TSC1-mTOR-Tau signaling. *Biochemical and biophysical research communications*498(1), 234-239. doi: 10.1016/j.bbrc.2018.02.201.

Li, J., Lin, H., Sun, Z., Kong, G., Yan, X., Wang, Y., et al. (2018b). High-Throughput Data of Circular RNA Profiles in Human Temporal Cortex Tissue Reveals Novel Insights into Temporal Lobe Epilepsy. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology*45(2), 677-691. doi: 10.1159/000487161.

Li, R., Wen, Y., Wu, B., He, M., Zhang, P., Zhang, Q., et al. (2020). MicroRNA-25-3p suppresses epileptiform discharges through inhibiting oxidative stress and apoptosis via targeting OXSR1 in neurons. *Biochemical and biophysical research communications*523(4), 859-866. doi: 10.1016/j.bbrc.2020.01.050.

Li, T., Jia, Y., Ma, C., Qiu, W., Wang, Q., Shao, X., et al. (2018c). The role of the microRNA-146a/complement factor H/interleukin-1β-mediated inflammatory loop circuit in the perpetuate inflammation of chronic temporal lobe epilepsy. *Disease models & mechanisms* 11(3). doi: 10.1242/dmm.031708.

Li, X., Gao, Z., Ma, M., Li, L., and Guo, S. (2022). Identification of serum miR-378 and miR-575 as diagnostic indicators and predicting surgical prognosis in human epilepsy. *Journal of medical biochemistry* 41(2), 184-190. doi: 10.5937/jomb0-32988.

Li, X., Giri, V., Cui, Y., Yin, M., Xian, Z., and Li, J. (2019b). LncRNA FTX inhibits hippocampal neuron apoptosis by regulating miR-21-5p/SOX7 axis in a rat model of temporal lobe epilepsy. *Biochemical and biophysical research communications* 512(1), 79-86. doi: 10.1016/j.bbrc.2019.03.019.

Li, Y., Huang, C., Feng, P., Jiang, Y., Wang, W., Zhou, D., et al. (2016). Aberrant expression of miR-153 is associated with overexpression of hypoxia-inducible factor-1α in refractory epilepsy. *Scientific reports* 6, 32091. doi: 10.1038/srep32091.

Lin, Q., Chen, J., Zheng, X., Zhang, Y., Tao, X., and Ye, J. (2020). Circular RNA Circ_ANKMY2 Regulates Temporal Lobe Epilepsy Progression via the miR-106b-5p/FOXP1 Axis. *Neurochemical research*45(12), 3034-3044. doi: 10.1007/s11064-020-03151-7.

Lipovich, L., Dachet, F., Cai, J., Bagla, S., Balan, K., Jia, H., et al. (2012). Activity-dependent human brain coding/noncoding gene regulatory networks. *Genetics* 192(3), 1133-1148. doi: 10.1534/genetics.112.145128.

Liu, A., Wu, Y., and Wang, Y. (2017a). MicroRNA-129-5p inhibits the development of autoimmune encephalomyelitis-related epilepsy by targeting HMGB1 through the TLR4/NF-kB signaling pathway. *Brain research bulletin* 132, 139-149. doi: 10.1016/j.brainresbull.2017.05.004.

Liu, D., Li, S., Gong, L., Yang, Y., Han, Y., Xie, M., et al. (2019a). Suppression of microRNA-141 suppressed p53 to protect against neural apoptosis in epilepsy by SIRT1 expression. *Journal of cellular biochemistry* 120(6), 9409-9420. doi: 10.1002/jcb.28216.

Liu, Q., Wang, L., Yan, G., Zhang, W., Huan, Z., and Li, J. (2019b). MiR-125a-5p Alleviates Dysfunction and Inflammation of Pentylenetetrazol- induced Epilepsy Through Targeting Calmodulin-dependent Protein Kinase IV (CAMK4). *Current neurovascular research* 16(4), 365-372. doi: 10.2174/1567202616666190906125444.

Liu, X., Geng, J., Guo, H., Zhao, H., and Ai, Y. (2020). Propofol inhibited apoptosis of hippocampal neurons in status epilepticus through miR-15a-5p/NR2B/ERK1/2 pathway. *Cell cycle (Georgetown, Tex.)*19(9), 1000-1011. doi: 10.1080/15384101.2020.1743909.

Liu, X., Liao, Y., Wang, X., Zou, D., Luo, C., Jian, C., et al. (2017b). MicroRNA expression profiles in chronic epilepsy rats and neuroprotection from seizures by targeting miR-344a.*Neuropsychiatric disease and treatment* 13, 2037-2044. doi: 10.2147/ndt.s141062.

Livneh, I., Moshitch-Moshkovitz, S., Amariglio, N., Rechavi, G., and Dominissini, D. (2020). The mA epitranscriptome: transcriptome plasticity in brain development and function. *Nature reviews. Neuroscience* 21(1), 36-51. doi: 10.1038/s41583-019-0244-z.

Longo, R., Peri, C., Cricrì, D., Coppi, L., Caruso, D., Mitro, N., et al. (2019). Ketogenic Diet: A New Light Shining on Old but Gold Biochemistry. *Nutrients* 11(10). doi: 10.3390/nu11102497.

Lu, J., Zhou, N., Yang, P., Deng, L., and Liu, G. (2019). MicroRNA-27a-3p Downregulation Inhibits Inflammatory Response and Hippocampal Neuronal Cell Apoptosis by Upregulating Mitogen-Activated Protein Kinase 4 (MAP2K4) Expression in Epilepsy: In Vivo and In Vitro Studies. *Medical science monitor : international medical journal of experimental and clinical research* 25, 8499-8508. doi: 10.12659/msm.916458.

Lunke, S., Maxwell, S., Khurana, I., K N, H., Okabe, J., Al-Hasani, K., et al. (2021). Epigenetic evidence of an Ac/Dc axis by VPA and SAHA.*Clinical epigenetics* 13(1), 58. doi: 10.1186/s13148-021-01050-4.

Lunyak, V., Burgess, R., Prefontaine, G., Nelson, C., Sze, S., Chenoweth, J., et al. (2002). Corepressor-dependent silencing of chromosomal regions encoding neuronal genes. *Science (New York, N.Y.)* 298(5599), 1747-1752. doi: 10.1126/science.1076469.

Lusardi, T., Akula, K., Coffman, S., Ruskin, D., Masino, S., and Boison, D. (2015). Ketogenic diet prevents epileptogenesis and disease progression in adult mice and rats. *Neuropharmacology*99, 500-509. doi: 10.1016/j.neuropharm.2015.08.007.

Lv, Y., Zheng, X., Shi, M., Wang, Z., and Cui, L. (2019). Different EPHX1 methylation levels in promoter area between carbamazepine-resistant epilepsy group and carbamazepine-sensitive epilepsy group in Chinese population. *BMC neurology*19(1), 114. doi: 10.1186/s12883-019-1308-4.

Ma, C., Chang, M., Lv, H., Zhang, Z., Zhang, W., He, X., et al. (2018). RNA mA methylation participates in regulation of postnatal development of the mouse cerebellum. *Genome biology* 19(1), 68. doi: 10.1186/s13059-018-1435-z.

Martins-Ferreira, R., Leal, B., Chaves, J., Li, T., Ciudad, L., Rangel, R., et al. (2021). Epilepsy progression is associated with cumulative DNA methylation changes in inflammatory genes. *Progress in neurobiology* 209, 102207. doi: 10.1016/j.pneurobio.2021.102207.

McClelland, S., Brennan, G., Dubé, C., Rajpara, S., Iyer, S., Richichi, C., et al. (2014). The transcription factor NRSF contributes to epileptogenesis by selective repression of a subset of target genes.*eLife* 3, e01267. doi: 10.7554/eLife.01267.

McClelland, S., Flynn, C., Dubé, C., Richichi, C., Zha, Q., Ghestem, A., et al. (2011). Neuron-restrictive silencer factor-mediated hyperpolarization-activated cyclic nucleotide gated channelopathy in experimental temporal lobe epilepsy. *Annals of neurology*70(3), 454-464. doi: 10.1002/ana.22479.

Merkurjev, D., Hong, W., Iida, K., Oomoto, I., Goldie, B., Yamaguti, H., et al. (2018). Synaptic N-methyladenosine (mA) epitranscriptome reveals functional partitioning of localized transcripts. *Nature neu-*

roscience 21(7), 1004-1014. doi: 10.1038/s41593-018-0173-6.

Metzger, E., Wissmann, M., Yin, N., Müller, J., Schneider, R., Peters, A., et al. (2005). LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature*437(7057), 436-439. doi: 10.1038/nature04020.

Miller-Delaney, S., Bryan, K., Das, S., McKiernan, R., Bray, I., Reynolds, J., et al. (2015). Differential DNA methylation profiles of coding and non-coding genes define hippocampal sclerosis in human temporal lobe epilepsy. *Brain : a journal of neurology*138, 616-631. doi: 10.1093/brain/awu373.

Modarresi, F., Faghihi, M., Lopez-Toledano, M., Fatemi, R., Magistri, M., Brothers, S., et al. (2012). Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. *Nature biotechnology* 30(5), 453-459. doi: 10.1038/nbt.2158.

Mooney, C., Becker, B., Raoof, R., and Henshall, D. (2016). EpimiRBase: a comprehensive database of microRNA-epilepsy associations.*Bioinformatics (Oxford, England)* 32(9), 1436-1438. doi: 10.1093/bioinformatics/btw008.

Morris, G., O'Brien, D., and Henshall, D. (2021). Opportunities and challenges for microRNA-targeting therapeutics for epilepsy.*Trends in pharmacological sciences* 42(7), 605-616. doi: 10.1016/j.tips.2021.04.007.

Morris, G., Reschke, C., and Henshall, D. (2019). Targeting microRNA-134 for seizure control and disease modification in epilepsy.*EBioMedicine* 45, 646-654. doi: 10.1016/j.ebiom.2019.07.008.

Moshé, S., Perucca, E., Ryvlin, P., and Tomson, T. (2015). Epilepsy: new advances. *Lancet (London, England)* 385(9971), 884-898. doi: 10.1016/s0140-6736(14)60456-6.

Mucha, M., Ooi, L., Linley, J., Mordaka, P., Dalle, C., Robertson, B., et al. (2010). Transcriptional control of KCNQ channel genes and the regulation of neuronal excitability. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 30(40),13235-13245. doi: 10.1523/jneurosci.1981-10.2010.

Mulligan, P., Westbrook, T., Ottinger, M., Pavlova, N., Chang, B., Macia, E., et al. (2008). CDYL bridges REST and histone methyltransferases for gene repression and suppression of cellular transformation. *Molecular cell* 32(5), 718-726. doi: 10.1016/j.molcel.2008.10.025.

Muraoka, Y., Nikaido, A., Kowada, R., Kimura, H., Yamaguchi, M., and Yoshida, H. (2021). Identification of Rpd3 as a novel epigenetic regulator of Drosophila FIG 4, a Charcot-Marie-Tooth disease-causing gene. *Neuroreport* 32(7), 562-568. doi: 10.1097/wnr.0000000000001636.

Murugan, M., and Boison, D. (2020). Ketogenic diet, neuroprotection, and antiepileptogenesis. *Epilepsy research* 167, 106444. doi: 10.1016/j.eplepsyres.2020.106444.

Navarrete-Modesto, V., Orozco-Suárez, S., Alonso-Vanegas, M., Feria-Romero, I., and Rocha, L. (2019). REST/NRSF transcription factor is overexpressed in hippocampus of patients with drug-resistant mesial temporal lobe epilepsy. *Epilepsy & behavior : E&B* 94,118-123. doi: 10.1016/j.yebeh.2019.02.012.

Nishiyama, A., and Nakanishi, M. (2021). Navigating the DNA methylation landscape of cancer. *Trends in genetics : TIG* 37(11),1012-1027. doi: 10.1016/j.tig.2021.05.002.

Niu, J., Wang, B., Wang, T., and Zhou, T. (2022). Mechanism of METTL3-mediated m6A modification in depression-induced cognitive deficits. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* 189, 86-99. doi: 10.1002/ajmg.b.32892.

Niu, X., Zhu, H., Liu, Q., Yan, J., and Li, M. (2021). MiR-194-5p serves as a potential biomarker and regulates the proliferation and apoptosis of hippocampus neuron in children with temporal lobe epilepsy.*Journal of the Chinese Medical Association : JCMA* 84(5),510-516. doi: 10.1097/jcma.0000000000000518.

Nomura, M., Uda-Tochio, H., Murai, K., Mori, N., and Nishimura, Y. (2005). The neural repressor NRSF/REST binds the PAH1 domain of the Sin3 corepressor by using its distinct short hydrophobic helix. *Journal of molecular biology* 354(4), 903-915. doi: 10.1016/j.jmb.2005.10.008.

Patterson, K., Barry, J., Curran, M., Singh-Taylor, A., Brennan, G., Rismanchi, N., et al. (2017). Enduring Memory Impairments Provoked by Developmental Febrile Seizures Are Mediated by Functional and Structural Effects of Neuronal Restrictive Silencing Factor. *The Journal of neuroscience : the official journal of the Society for Neuroscience*37(14), 3799-3812. doi: 10.1523/jneurosci.3748-16.2017.

Pensold, D., Reichard, J., Van Loo, K., Ciganok, N., Hahn, A., Bayer, C., et al. (2020). DNA Methylation-Mediated Modulation of Endocytosis as Potential Mechanism for Synaptic Function Regulation in Murine Inhibitory Cortical Interneurons. *Cerebral cortex (New York, N.Y. : 1991)* 30(7), 3921-3937. doi: 10.1093/cercor/bhaa009.

Phiel, C., Zhang, F., Huang, E., Guenther, M., Lazar, M., and Klein, P. (2001). Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *The Journal of biological chemistry* 276(39), 36734-36741. doi: 10.1074/jbc.M101287200.

Poeta, L., Padula, A., Lioi, M., van Bokhoven, H., and Miano, M. (2021). Analysis of a Set of KDM5C Regulatory Genes Mutated in Neurodevelopmental Disorders Identifies Temporal Coexpression Brain Signatures. *Genes* 12(7). doi: 10.3390/genes12071088.

Portales-Casamar, E., Lussier, A., Jones, M., MacIsaac, J., Edgar, R., Mah, S., et al. (2016). DNA methylation signature of human fetal alcohol spectrum disorder. *Epigenetics & chromatin* 9, 25. doi: 10.1186/s13072-016-0074-4.

Qi, Y., Qian, R., Jia, L., Fei, X., Zhang, D., Zhang, Y., et al. (2020). Overexpressed microRNA-494 represses RIPK1 to attenuate hippocampal neuron injury in epilepsy rats by inactivating the NF-ϰB signaling pathway. *Cell cycle (Georgetown, Tex.)* 19(11),1298-1313. doi: 10.1080/15384101.2020.1749472.

Reddy, S., Clossen, B., and Reddy, D. (2018). Epigenetic Histone Deacetylation Inhibition Prevents the Development and Persistence of Temporal Lobe Epilepsy. *The Journal of pharmacology and experimental therapeutics* 364(1), 97-109. doi: 10.1124/jpet.117.244939.

Riaz, S., Saeed, M., and Malik, M. (2015). Clinical and Therapeutic Implications of Histone Acetylation in Breast Cancer. *The West Indian medical journal* 65(2), 337-344. doi: 10.7727/wimj.2014.297.

Roopra, A., Qazi, R., Schoenike, B., Daley, T., and Morrison, J. (2004). Localized domains of G9a-mediated histone methylation are required for silencing of neuronal genes. *Molecular cell* 14(6),727-738. doi: 10.1016/j.molcel.2004.05.026.

Rowles, J., Wong, M., Powers, R., and Olsen, M. (2012). FTO, RNA epigenetics and epilepsy. *Epigenetics* 7(10), 1094-1097. doi: 10.4161/epi.21977.

Rusconi, F., Paganini, L., Braida, D., Ponzoni, L., Toffolo, E., Maroli, A., et al. (2015). LSD1 Neurospecific Alternative Splicing Controls Neuronal Excitability in Mouse Models of Epilepsy. *Cerebral cortex (New York, N.Y. : 1991)* 25(9), 2729-2740. doi: 10.1093/cercor/bhu070.

Ryley Parrish, R., Albertson, A., Buckingham, S., Hablitz, J., Mascia, K., Davis Haselden, W., et al. (2013). Status epilepticus triggers early and late alterations in brain-derived neurotrophic factor and NMDA glutamate receptor Grin2b DNA methylation levels in the hippocampus.*Neuroscience* 248, 602-619. doi: 10.1016/j.neuroscience.2013.06.029.

Sáez, M., Fernández-Rodríguez, J., Moutinho, C., Sanchez-Mut, J., Gomez, A., Vidal, E., et al. (2016). Mutations in JMJD1C are involved in Rett syndrome and intellectual disability. *Genetics in medicine : official journal of the American College of Medical Genetics*18(4), 378-385. doi: 10.1038/gim.2015.100.

Shein, N., Grigoriadis, N., Alexandrovich, A., Simeonidou, C., Lourbopoulos, A., Polyzoidou, E., et al. (2009). Histone deacetylase inhibitor ITF2357 is neuroprotective, improves functional recovery, and induces glial apoptosis following experimental traumatic brain injury.*FASEB journal : official publication of the Federation of American Societies for Experimental Biology* 23(12), 4266-4275. doi: 10.1096/fj.09-134700.

Shen, T., Ji, F., Yuan, Z., and Jiao, J. (2015). CHD2 is Required for Embryonic Neurogenesis in the Developing Cerebral Cortex. *Stem cells (Dayton, Ohio)* 33(6), 1794-1806. doi: 10.1002/stem.2001.

Shi, H., Zhang, X., Weng, Y., Lu, Z., Liu, Y., Lu, Z., et al. (2018). mA facilitates hippocampus-dependent learning and memory through YTHDF1.*Nature* 563(7730), 249-253. doi: 10.1038/s41586-018-0666-1.

Shimojo, M., and Hersh, L. (2006). Characterization of the REST/NRSF-interacting LIM domain protein (RILP): localization and interaction with REST/NRSF. *Journal of neurochemistry*96(4), 1130-1138. doi: 10.1111/j.1471-4159.2005.03608.x.

Sng, J., Taniura, H., and Yoneda, Y. (2006). Histone modifications in kainate-induced status epilepticus. *The European journal of neuroscience* 23(5), 1269-1282. doi: 10.1111/j.1460-9568.2006.04641.x.

Soga, T., Nakajima, S., Kawaguchi, M., and Parhar, I. (2021). Repressor element 1 silencing transcription factor /neuron-restrictive silencing factor (REST/NRSF) in social stress and depression. *Progress in neuropsychopharmacology & biological psychiatry* 104, 110053. doi: 10.1016/j.pnpbp.2020.110053.

Spencer, E., Chandler, K., Haddley, K., Howard, M., Hughes, D., Belyaev, N., et al. (2006). Regulation and role of REST and REST4 variants in modulation of gene expression in in vivo and in vitro in epilepsy models. *Neurobiology of disease* 24(1), 41-52. doi: 10.1016/j.nbd.2006.04.020.

Su, W., Aloi, M., and Garden, G. (2016). MicroRNAs mediating CNS inflammation: Small regulators with powerful potential. *Brain, behavior, and immunity* 52, 1-8. doi: 10.1016/j.bbi.2015.07.003.

Su, X., Shen, B., Wang, K., Song, Q., Yang, X., Wu, D., et al. (2022a). Roles of the Neuron-Restrictive Silencer Factor in the Pathophysiological Process of the Central Nervous System.*Frontiers in cell and developmental biology* 10, 834620. doi: 10.3389/fcell.2022.834620.

Su, Z., Li, Y., Chen, S., Liu, X., Zhao, K., Peng, Y., et al. (2022b). Identification of Ion Channel-Related Genes and miRNA-mRNA Networks in Mesial Temporal Lobe Epilepsy. *Frontiers in genetics* 13,853529. doi: 10.3389/fgene.2022.853529.

Tan, C., Plotkin, J., Venø, M., von Schimmelmann, M., Feinberg, P., Mann, S., et al. (2013). MicroRNA-128 governs neuronal excitability and motor behavior in mice. *Science (New York, N.Y.)*342(6163), 1254-1258. doi: 10.1126/science.1244193.

Tan, N., Tang, H., Lin, G., Chen, Y., Lu, P., Li, H., et al. (2017). Epigenetic Downregulation of Scn3a Expression by Valproate: a Possible Role in Its Anticonvulsant Activity. *Molecular neurobiology*54(4), 2831-2842. doi: 10.1007/s12035-016-9871-9.

Tang, C., Gu, Y., Wang, H., Wu, H., Wang, Y., Meng, Y., et al. (2018). Targeting of microRNA-21-5p protects against seizure damage in a kainic acid-induced status epilepticus model via PTEN-mTOR. *Epilepsy research* 144, 34-42. doi: 10.1016/j.eplepsyres.2018.05.001.

Tao, N., Wen, T., Li, T., Luan, L., Pan, H., and Wang, Y. (2022). Interaction between m6A methylation and noncoding RNA in glioma.*Cell death discovery* 8(1), 283. doi: 10.1038/s41420-022-01075-5.

Tapias, A., Lázaro, D., Yin, B., Rasa, S., Krepelova, A., Kelmer Sacramento, E., et al. (2021). HAT cofactor TRRAP modulates microtubule dynamics via SP1 signaling to prevent neurodegeneration. *eLife*10. doi: 10.7554/eLife.61531.

Tapias, A., Zhou, Z., Shi, Y., Chong, Z., Wang, P., Groth, M., et al. (2014). Trrap-dependent histone acetylation specifically regulates cell-cycle gene transcription to control neural progenitor fate decisions. *Cell stem cell* 14(5), 632-643. doi: 10.1016/j.stem.2014.04.001.

Thompson, R., and Chan, C. (2018). NRSF and Its Epigenetic Effectors: New Treatments for Neurological Disease. *Brain sciences* 8(12). doi: 10.3390/brainsci8120226.

Tsankova, N., Kumar, A., and Nestler, E. (2004). Histone modifications at gene promoter regions in rat hippocampus after acute and chronic electroconvulsive seizures. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 24(24),5603-5610. doi: 10.1523/jneurosci.0589-04.2004.

Ünalp, A., Coskunpinar, E., Gunduz, K., Pekuz, S., Baysal, B., Edizer, S., et al. (2022). Detection of Deregulated miRNAs in Childhood Epileptic Encephalopathies. *Journal of molecular neuroscience : MN* 72(6), 1234-1242. doi: 10.1007/s12031-022-02001-1.

Vangoor, V., Reschke, C., Senthilkumar, K., van de Haar, L., de Wit, M., Giuliani, G., et al. (2019). miR-135aAntagonizing Increased Levels at the Chronic Stage of Experimental TLE Reduces Spontaneous Recurrent Seizures. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 39(26), 5064-5079. doi: 10.1523/jneurosci.3014-18.2019.

Vermeulen, M., Eberl, H., Matarese, F., Marks, H., Denissov, S., Butter, F., et al. (2010). Quantitative interaction proteomics and genome-wide profiling of epigenetic histone marks and their readers. *Cell*142(6), 967-980. doi: 10.1016/j.cell.2010.08.020.

Villa, C., Lavitrano, M., and Combi, R. (2019). Long Non-Coding RNAs and Related Molecular Pathways in the Pathogenesis of Epilepsy.*International journal of molecular sciences* 20(19). doi: 10.3390/ijms20194898.

Walters, B., Mercaldo, V., Gillon, C., Yip, M., Neve, R., Boyce, F., et al. (2017). The Role of The RNA Demethylase FTO (Fat Mass and Obesity-Associated) and mRNA Methylation in Hippocampal Memory Formation. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 42(7), 1502-1510. doi: 10.1038/npp.2017.31.

Wan, Y., and Yang, Z. (2020). LncRNA NEAT1 affects inflammatory response by targeting miR-129-5p and regulating Notch signaling pathway in epilepsy. *Cell cycle (Georgetown, Tex.)* 19(4), 419-431. doi: 10.1080/15384101.2020.1711578.

Wang, C., Cui, G., Liu, X., Xu, K., Wang, M., Zhang, X., et al. (2018a). METTL3-mediated m6A modification is required for cerebellar development.*PLoS biology* 16(6), e2004880. doi: 10.1371/journal.pbio.2004880.

Wang, D., Li, Z., Zhang, Y., Wang, G., Wei, M., Hu, Y., et al. (2016a). Targeting of microRNA-199a-5p protects against pilocarpine-induced status epilepticus and seizure damage via SIRT1-p53 cascade.*Epilepsia* 57(5), 706-716. doi: 10.1111/epi.13348.

Wang, G., Luan, Z., Che, N., Yan, D., Sun, X., Zhang, C., et al. (2021a). Inhibition of microRNA-129-2-3p protects against refractory temporal lobe epilepsy by regulating GABRA1. *Brain and behavior*11(7), e02195. doi: 10.1002/brb3.2195.

Wang, H., Yan, H., Wang, K., and Wang, J. (2017). Dynamic regulation effect of long non-coding RNA-UCA1 on NF-kB in hippocampus of epilepsy rats. *European review for medical and pharmacological sciences*21(13), 3113-3119.

Wang, J., Zheng, Y., Cheng, X., Xu, F., Zhang, P., Zhou, X., et al. (2019a). Inhibition of microRNA-34a Suppresses Epileptiform Discharges Through Regulating Notch Signaling and Apoptosis in Cultured Hippocampal Neurons. *Neurochemical research* 44(5), 1252-1261. doi: 10.1007/s11064-019-02772-x.

Wang, L., Fu, X., Peng, X., Xiao, Z., Li, Z., Chen, G., et al. (2016b). DNA Methylation Profiling Reveals Correlation of Differential Methylation Patterns with Gene Expression in Human Epilepsy.*Journal of molecular neuroscience : MN* 59(1), 68-77. doi: 10.1007/s12031-016-0735-6.

Wang, L., Song, L., Chen, X., Ma, Y., Suo, J., Shi, J., et al. (2019b). MiR-181b inhibits P38/JNK signaling pathway to attenuate autophagy and apoptosis in juvenile rats with kainic acid-induced epilepsy via targeting TLR4. *CNS neuroscience & therapeutics* 25(1),112-122. doi: 10.1111/cns.12991.

Wang, P., Zhang, Y., Wang, Z., Yang, A., Li, Y., and Zhang, Q. (2021b). miR-128 regulates epilepsy sensitivity in mice by suppressing SNAP-25 and SYT1 expression in the hippocampus. *Biochemical and biophysical research communications* 545**,** 195-202. doi: 10.1016/j.bbrc.2021.01.079.

Wang, W., Guo, Y., He, L., Chen, C., Luo, J., Ma, Y., et al. (2018b). Overexpression of miRNA-137 in the brain suppresses seizure activity and neuronal excitability: A new potential therapeutic strategy for epilepsy. *Neuropharmacology* 138**,** 170-181. doi: 10.1016/j.neuropharm.2018.06.010.

Wang, W., Wang, X., Chen, L., Zhang, Y., Xu, Z., Liu, J., et al. (2016c). The microRNA miR-124 suppresses seizure activity and regulates CREB1 activity. *Expert reviews in molecular medicine* 18**,**e4. doi: 10.1017/erm.2016.3.

Wang, Y., Yang, Z., Zhang, K., Wan, Y., Zhou, Y., and Yang, Z. (2021c). miR-135a-5p inhibitor protects glial cells against apoptosis via targeting SIRT1 in epilepsy. *Experimental and therapeutic medicine* 21(5)**,** 431. doi: 10.3892/etm.2021.9848.

Wang, Z., Qu, J., Yang, Z., Liu, D., Jiang, S., Zhang, Y., et al. (2022). Integrated Analysis of Expression Profile and Potential Pathogenic Mechanism of Temporal Lobe Epilepsy With Hippocampal Sclerosis. *Frontiers in neuroscience* 16**,** 892022. doi: 10.3389/fnins.2022.892022.

Wawruszak, A., Halasa, M., Okon, E., Kukula-Koch, W., and Stepulak, A. (2021). Valproic Acid and Breast Cancer: State of the Art in 2021.*Cancers* 13(14). doi: 10.3390/cancers13143409.

Weerts, M., Lanko, K., Guzmán-Vega, F., Jackson, A., Ramakrishnan, R., Cardona-Londoño, K., et al. (2021). Delineating the molecular and phenotypic spectrum of the SETD1B-related syndrome. *Genetics in medicine : official journal of the American College of Medical Genetics*23(11)**,** 2122-2137. doi: 10.1038/s41436-021-01246-2.

Wei, G., Deng, X., Agarwal, S., Iwase, S., Disteche, C., and Xu, J. (2016). Patient Mutations of the Intellectual Disability Gene KDM5C Downregulate Netrin G2 and Suppress Neurite Growth in Neuro2a Cells.*Journal of molecular neuroscience : MN* 60(1)**,** 33-45. doi: 10.1007/s12031-016-0770-3.

Weng, N., Sun, J., Kuang, S., Lan, H., He, Q., Yang, H., et al. (2020). MicroRNA-451 Aggravates Kainic Acid-induced Seizure and Neuronal Apoptosis by Targeting GDNF. *Current neurovascular research*17(1)**,** 50-57. doi: 10.2174/1567202617666191223150510.

Westbrook, T., Hu, G., Ang, X., Mulligan, P., Pavlova, N., Liang, A., et al. (2008). SCFbeta-TRCP controls oncogenic transformation and neural differentiation through REST degradation. *Nature*452(7185)**,** 370-374. doi: 10.1038/nature06780.

Whittle, J., Powell, M., Popov, V., Shirley, L., Wang, C., and Pestell, R. (2007). Sirtuins, nuclear hormone receptor acetylation and transcriptional regulation. *Trends in endocrinology and metabolism: TEM* 18(9)**,** 356-364. doi: 10.1016/j.tem.2007.07.007.

Williams-Karnesky, R., Sandau, U., Lusardi, T., Lytle, N., Farrell, J., Pritchard, E., et al. (2013). Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. *The Journal of clinical investigation* 123(8)**,** 3552-3563. doi: 10.1172/jci65636.

Wilson, M., Henshall, D., Byrne, S., and Brennan, G. (2021). CHD2-Related CNS Pathologies. *International journal of molecular sciences* 22(2). doi: 10.3390/ijms22020588.

Wu, J., and Xie, X. (2006). Comparative sequence analysis reveals an intricate network among REST, CREB and miRNA in mediating neuronal gene expression. *Genome biology* 7(9)**,** R85. doi: 10.1186/gb-2006-7-9-r85.

Wu, P., Zuo, X., Deng, H., Liu, X., Liu, L., and Ji, A. (2013). Roles of long noncoding RNAs in brain development, functional diversification and neurodegenerative diseases. *Brain research bulletin* 97**,**69-80. doi: 10.1016/j.brainresbull.2013.06.001.

Wu, Q., and Yi, X. (2018). Down-regulation of Long Noncoding RNA MALAT1 Protects Hippocampal Neurons Against Excessive Autophagy and Apoptosis via the PI3K/Akt Signaling Pathway in Rats with Epilepsy. *Journal of molecular neuroscience : MN* 65(2), 234-245. doi: 10.1007/s12031-018-1093-3.

Wu, Y., Zhang, Y., Zhu, S., Tian, C., and Zhang, Y. (2021). MiRNA-29a serves as a promising diagnostic biomarker in children with temporal lobe epilepsy and regulates seizure-induced cell death and inflammation in hippocampal neurons. *Epileptic disorders : international epilepsy journal with videotape* 23(6), 823-832. doi: 10.1684/epd.2021.1331.

Xiang, L., Ren, Y., Cai, H., Zhao, W., and Song, Y. (2015). MicroRNA-132 aggravates epileptiform discharges via suppression of BDNF/TrkB signaling in cultured hippocampal neurons. *Brain research*1622, 484-495. doi: 10.1016/j.brainres.2015.06.046.

Xiang, L., Ren, Y., Li, X., Zhao, W., and Song, Y. (2016). MicroRNA-204 suppresses epileptiform discharges through regulating TrkB-ERK1/2-CREB signaling in cultured hippocampal neurons. *Brain research*1639, 99-107. doi: 10.1016/j.brainres.2016.02.045.

Xiao, D., Lv, J., Zheng, Z., Liu, Y., Zhang, Y., Luo, C., et al. (2021). Mechanisms of microRNA-142 in mitochondrial autophagy and hippocampal damage in a rat model of epilepsy. *International journal of molecular medicine* 47(6). doi: 10.3892/ijmm.2021.4931.

Xiao, W., Cao, Y., Long, H., Luo, Z., Li, S., Deng, N., et al. (2018). Genome-Wide DNA Methylation Patterns Analysis of Noncoding RNAs in Temporal Lobe Epilepsy Patients. *Molecular neurobiology*55(1), 793-803. doi: 10.1007/s12035-016-0353-x.

Xiaoying, G., Guo, M., Jie, L., Yanmei, Z., Ying, C., Shengjie, S., et al. (2020). CircHivep2 contributes to microglia activation and inflammation via miR-181a-5p/SOCS2 signalling in mice with kainic acid-induced epileptic seizures. *Journal of cellular and molecular medicine* 24(22), 12980-12993. doi: 10.1111/jcmm.15894.

Xie, H., Liu, X., Zhou, Q., Huang, T., Zhang, L., Gao, J., et al. (2022). DNA Methylation Modulates Aging Process in Adipocytes.*Aging and disease* 13(2), 433-446. doi: 10.14336/ad.2021.0904.

Xu, Y., Wang, Y., Yan, S., Yang, Q., Zhou, Y., Zeng, X., et al. (2017). Regulation of endothelial intracellular adenosine via adenosine kinase epigenetically modulates vascular inflammation. *Nature communications* 8(1), 943. doi: 10.1038/s41467-017-00986-7.

Yan, Y., Xia, H., Hu, J., and Zhang, B. (2019). MicroRNA-542-3p Regulates P-glycoprotein Expression in Rat Epilepsy via the Toll-like Receptor 4/Nuclear Factor-kappaB Signaling Pathway. *Current neurovascular research* 16(5), 433-440. doi: 10.2174/1567202616666191023160201.

Yang, M., Gocke, C., Luo, X., Borek, D., Tomchick, D., Machius, M., et al. (2006). Structural basis for CoREST-dependent demethylation of nucleosomes by the human LSD1 histone demethylase. *Molecular cell*23(3), 377-387. doi: 10.1016/j.molcel.2006.07.012.

Yang, Y., Shuai, P., Li, X., Sun, K., Jiang, X., Liu, W., et al. (2022). Mettl14-mediated m6A modification is essential for visual function and retinal photoreceptor survival. *BMC biology* 20(1), 140. doi: 10.1186/s12915-022-01335-x.

Yao, R., Wang, Y., and Chen, L. (2019). Cellular functions of long noncoding RNAs. *Nature cell biology* 21(5), 542-551. doi: 10.1038/s41556-019-0311-8.

You, Y., Fu, Y., Huang, M., Shen, D., Zhao, B., Liu, H., et al. (2022). Recent Advances of m6A Demethylases Inhibitors and Their Biological Functions in Human Diseases. *International journal of molecular sciences* 23(10). doi: 10.3390/ijms23105815.

Younus, I., and Reddy, D. (2017). Epigenetic interventions for epileptogenesis: A new frontier for curing epilepsy. *Pharmacology & therapeutics* 177, 108-122. doi: 10.1016/j.pharmthera.2017.03.002.

Yu, J., Chen, M., Huang, H., Zhu, J., Song, H., Zhu, J., et al. (2018). Dynamic m6A modification regulates local translation of mRNA in axons.*Nucleic acids research* 46(3), 1412-1423. doi: 10.1093/nar/gkx1182.

Yu, Q., Zhao, M., and Yang, P. (2020). LncRNA UCA1 Suppresses the Inflammation Via Modulating miR-203-Mediated Regulation of MEF2C/NF-κB Signaling Pathway in Epilepsy. *Neurochemical research*45(4), 783-795. doi: 10.1007/s11064-019-02952-9.

Yu, Y., Du, L., and Zhang, J. (2021). Febrile Seizure-Related miR-148a-3p Exerts Neuroprotection by Promoting the Proliferation of Hippocampal Neurons in Children with Temporal Lobe Epilepsy.*Developmental neuroscience* 43(5), 312-320. doi: 10.1159/000518352.

Zhang, B., West, E., Van, K., Gurkoff, G., Zhou, J., Zhang, X., et al. (2008). HDAC inhibitor increases histone H3 acetylation and reduces microglia inflammatory response following traumatic brain injury in rats. *Brain research* 1226, 181-191. doi: 10.1016/j.brainres.2008.05.085.

Zhang, H., Qu, Y., and Wang, A. (2018a). Antagonist targeting microRNA-146a protects against lithium-pilocarpine-induced status epilepticus in rats by nuclear factor-κB pathway. *Molecular medicine reports* 17(4), 5356-5361. doi: 10.3892/mmr.2018.8465.

Zhang, L., Li, Y., Ye, X., and Bian, L. (2018b). Bioinformatics Analysis of Microarray Profiling Identifies That the miR-203-3p Target Ppp2ca Aggravates Seizure Activity in Mice. *Journal of molecular neuroscience : MN* 66(1), 146-154. doi: 10.1007/s12031-018-1145-8.

Zhang, M., Yang, H., Chen, Z., Hu, X., Wu, T., and Liu, W. (2021). Long Noncoding RNA X-Inactive-Specific Transcript Promotes the Secretion of Inflammatory Cytokines in LPS Stimulated Astrocyte Cell Via Sponging miR-29c-3p and Regulating Nuclear Factor of Activated T cell 5 Expression. *Frontiers in endocrinology* 12, 573143. doi: 10.3389/fendo.2021.573143.

Zhang, S., Zhang, M., Tao, H., Luo, Y., He, T., Wang, C., et al. (2018c). Dimethylation of Histone 3 Lysine 9 is sensitive to the epileptic activity, and affects the transcriptional regulation of the potassium channel Kcnj10 gene in epileptic rats. *Molecular medicine reports* 17(1), 1368-1374. doi: 10.3892/mmr.2017.7942.

Zhang, X., Li, X., Li, B., Sun, C., and Zhang, P. (2020). miR-21-5p protects hippocampal neurons of epileptic rats via inhibiting STAT3 expression. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University* 29(7), 793-801. doi: 10.17219/acem/121929.

Zhang, Z., Wang, M., Xie, D., Huang, Z., Zhang, L., Yang, Y., et al. (2018d). METTL3-mediated N-methyladenosine mRNA modification enhances long-term memory consolidation. *Cell research* 28(11),1050-1061. doi: 10.1038/s41422-018-0092-9.

Zhao, C., Liu, D., Fan, Y., and Wu, J. (2022). LncRNA GAS5 promotes epilepsy progression through the epigenetic repression of miR-219, in turn affecting CaMKIIγ/NMDAR pathway. *Journal of neurogenetics*36(1), 32-42. doi: 10.1080/01677063.2022.2067536.

Zhao, C., Yang, F., Wei, X., and Zhang, J. (2021). miR-139-5p upregulation alleviated spontaneous recurrent epileptiform discharge-induced oxidative stress and apoptosis in rat hippocampal neurons via regulating the Notch pathway. *Cell biology international* 45(2), 463-476. doi: 10.1002/cbin.11509.

Zhao, M., Qiu, W., and Yang, P. (2020). SP1 activated-lncRNA SNHG1 mediates the development of epilepsy via miR-154-5p/TLR5 axis.*Epilepsy research* 168, 106476. doi: 10.1016/j.eplepsyres.2020.106476.

Zhao, Q., Yin, C., Yuan, Y., Zhang, H., and Teng, L. (2019a). Down-Regulation of Mir-145 Improves Learning and Memory Abilities in Epileptic Rats by Regulating Hippocampal Neuron Apoptosis. *World neurosurgery* 122, e1432-e1438. doi: 10.1016/j.wneu.2018.11.080.

Zhao, T., Ding, Y., Li, M., Zhou, C., and Lin, W. (2019b). Silencing lncRNA PVT1 inhibits activation of astrocytes and increases BDNF expression in hippocampus tissues of rats with epilepsy by downregulating the Wnt signaling pathway. *Journal of cellular physiology* . doi: 10.1002/jcp.28264.

Zheng, D., Li, M., Li, G., Hu, J., Jiang, X., Wang, Y., et al. (2021). Circular RNA circ_DROSHA alleviates the neural damage in a cell model of temporal lobe epilepsy through regulating miR-106b-5p/MEF2C axis.*Cellular signalling* 80**,** 109901. doi: 10.1016/j.cellsig.2020.109901.

Zheng, H., Tang, R., Yao, Y., Ji, Z., Cao, Y., Liu, Z., et al. (2016). MiR-219 Protects Against Seizure in the Kainic Acid Model of Epilepsy.*Molecular neurobiology* 53(1)**,** 1-7. doi: 10.1007/s12035-014-8981-5.

Zheng, P., Bin, H., and Chen, W. (2019). Inhibition of microRNA-103a inhibits the activation of astrocytes in hippocampus tissues and improves the pathological injury of neurons of epilepsy rats by regulating BDNF. *Cancer cell international* 19(1)**,** 109. doi: 10.1186/s12935-019-0821-2.

Zhou, Q., Wang, Q., He, B., Kong, H., Luo, H., Wang, X., et al. (2022). MicroRNA 322-5p reduced neuronal inflammation via the TLR4/TRAF6/NF-ϰB axis in a rat epilepsy model. *Open medicine (Warsaw, Poland)*17(1)**,** 907-914. doi: 10.1515/med-2022-0485.

Zhu, Q., Wang, L., Zhang, Y., Zhao, F., Luo, J., Xiao, Z., et al. (2012). Increased expression of DNA methyltransferase 1 and 3a in human temporal lobe epilepsy. *Journal of molecular neuroscience : MN*46(2)**,** 420-426. doi: 10.1007/s12031-011-9602-7.

Zhu, X., Yao, Y., Liu, Y., Zhou, R., Zhang, W., Hu, Q., et al. (2019a). Regulation of ADAM10 by MicroRNA-23a Contributes to Epileptogenesis in Pilocarpine-Induced Status Epilepticus Mice. *Frontiers in cellular neuroscience* 13**,** 180. doi: 10.3389/fncel.2019.00180.

Zhu, X., Zhang, A., Dong, J., Yao, Y., Zhu, M., Xu, K., et al. (2019b). MicroRNA-23a contributes to hippocampal neuronal injuries and spatial memory impairment in an experimental model of temporal lobe epilepsy.*Brain research bulletin* 152**,** 175-183. doi: 10.1016/j.brainresbull.2019.07.021.

Zhu, Y., Li, C., Wang, Y., and Zhou, S. (2015). Change of MicroRNA-134, CREB and p-CREB expression in epileptic rat. *Asian Pacific journal of tropical medicine* 8(4)**,** 292-298. doi: 10.1016/s1995-7645(14)60333-3.

Zhu, Z., Wang, S., Cao, Q., and Li, G. (2021). CircUBQLN1 Promotes Proliferation but Inhibits Apoptosis and Oxidative Stress of Hippocampal Neurons in Epilepsy via the miR-155-Mediated SOX7 Upregulation.*Journal of molecular neuroscience : MN* 71(9)**,** 1933-1943. doi: 10.1007/s12031-021-01838-2.

Zybura-Broda, K., Amborska, R., Ambrozek-Latecka, M., Wilemska, J., Bogusz, A., Bucko, J., et al. (2016). Epigenetics of Epileptogenesis-Evoked Upregulation of Matrix Metalloproteinase-9 in Hippocampus. *PloS one* 11(8)**,** e0159745. doi: 10.1371/journal.pone.0159745.

Figure legends

Figure1. DNA methylation

In the catalysis of DNA methyltransferases (DNMT1, DNMT3a and DNMT3b), a methyl (CH_3) group is added into a cytosine base, which occurs mainly in CpGs. DNA methylation require the transfer of a methyl group from SAM resulting in the formation of SAH, which is then cleaved into adenosine and homocysteine.

Figure2. Histone modifications

Histone modifications mainly include histone acetylation and histone methylation. HDACs and HATs are necessary enzymes for histone acetylation. HATs catalyze the reversible acetylation reaction at the ε-amino group of lysine residues. Meanwhile, HDACs can remove acetyl groups silencing the transcriptional activity of genes and leading to chromatin condensation. Histone methylation is catalyzed by HMTs, which occurs mainly on lysine (K) and arginine (R) residues. Key enzymes of histone methylation involved in HMTs and KDMs. Lysine methylation occurs in mono-, di-, and tri-states, whereas arginine methylation only occurs in mono-and di-states. Histone H3 methylation occurs at lysine residues K4, K9, K27, K36, and K79 and histone H4 methylation occurs at lysine residues K20.

Figure1. DNA methylation

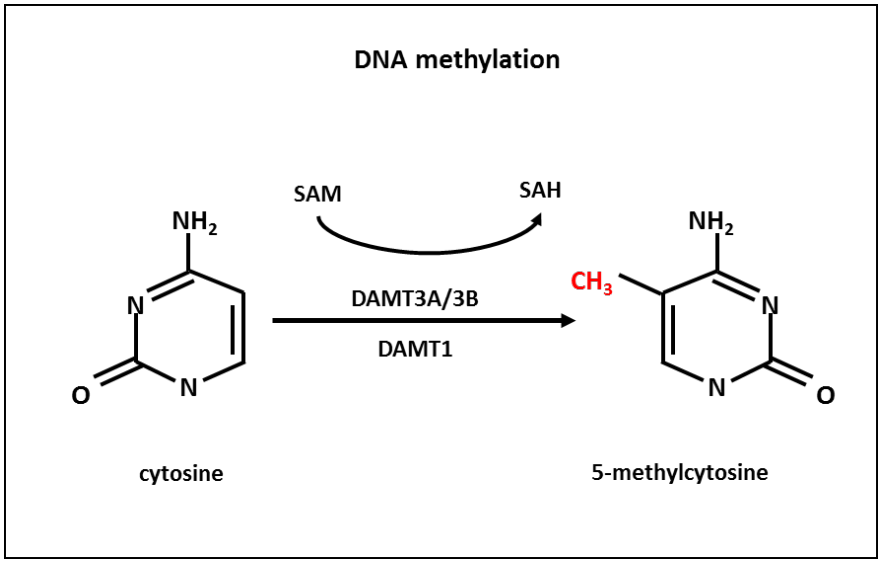


Figure2. Histone modifications

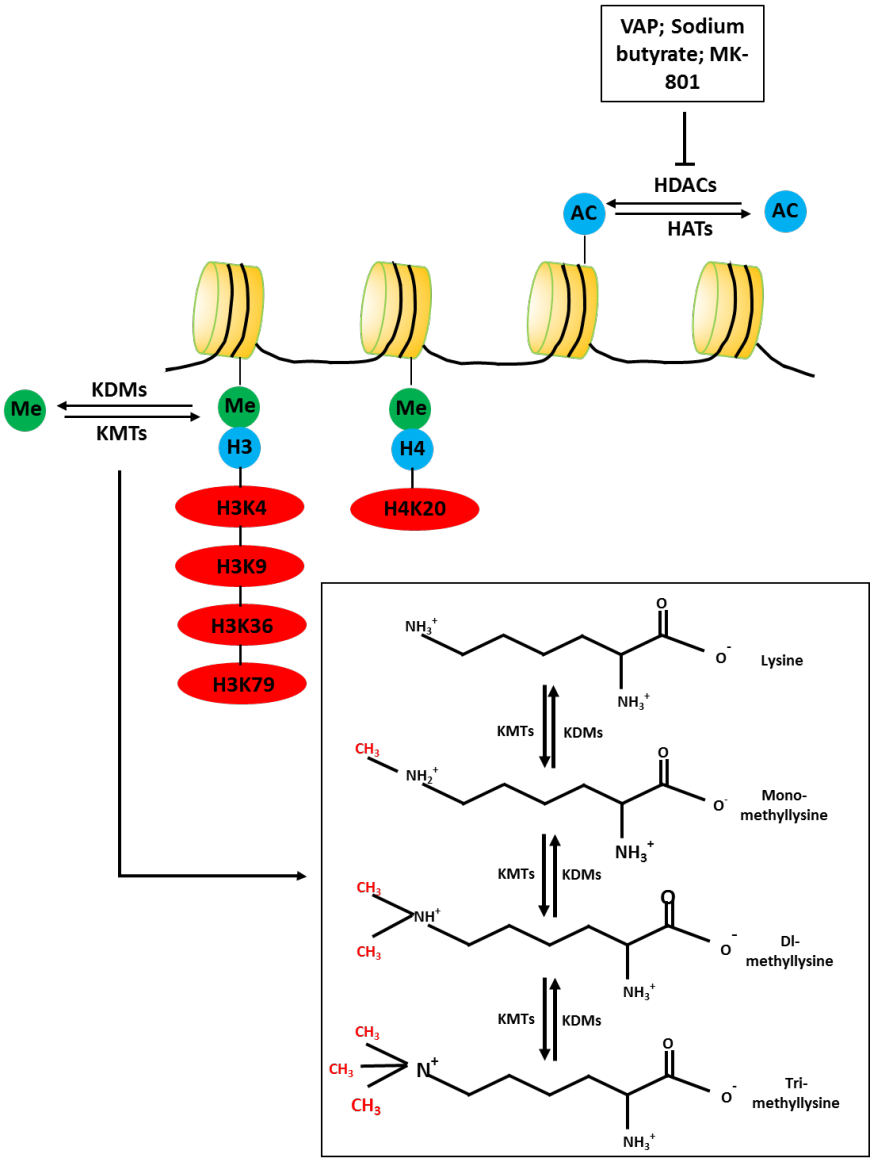


Table1. Regulation of microRNAs in epilepsy.

MicroRNAs	**Expression**	**Mechanisms**	**References**
MicroRNA-15a	Downregulation (pilocarpine, Mg^{2+} -free medium)	MicroRNA-15a targets GFAP to inhibit inflammation and apoptosis of hippocampal neurons by downregulating GFAP in pilocarpine-induced epilepsy rat model and Mg^{2+}-free medium treated TLE cell model. Propofol regulates microRNA-15a-5p/GluN2B/ERK1/2 pathway to suppress apoptosis hippocampal neuronal apoptosis in Mg^{2+} -free medium treated epilepsy cell model.	(Fan et al., 2020; Liu et al., 2020)
MicroRNA-20a-5p	Upregulation (PTZ)	MicroRNA-20a-5p is involved in synaptic plasticity and silencing microRNA-20a-5p inhibits neuronal branching and axonal growth and prevents epileptogenesis by regulating RGMa-RhoA-mediated synaptic plasticity in the PTZ-induced epilepsy model.	(Feng et al., 2020)

MicroRNAs	Expression	Mechanisms	References
MicroRNA-21-5p	Upregulation (electrical kindling, KA, pilocarpine)	MicroRNA-21-5p reduces IL-6 levels, loss of hippocampal neurons and apoptosis by inhibiting STAT3 expression, which suggesting protective effects of microRNA-21-5p in hippocampal neurons of epileptic rats. In KA-induced SE models, targeting of microRNA-21-5p also protects against seizure-induced injury by PTEN-mTOR.	(Tang et al., 2018; Zhang et al., 2020)
MicroRNA-22	Downregulation (KA, pilocarpine)	MicroRNA-22 inhibit neuroinflammatory signaling to protect against the development of epileptogenic brain networks. MicroRNA-22 prevents inflammation and development of epileptogenic focus by targeting P2X7R in the brain and microRNA-22 regulates aberrant neurogenesis and changes in neuronal morphology after SE in KA-induced epilepsy mice model.	(Jimenez-Mateos et al., 2015; Beamer et al., 2018; Almeida Silva et al., 2020)
MicroRNA-23a	Upregulation (KA, pilocarpine)	MicroRNA-23a is involved in hippocampal neuron injury, hippocampal oxidative damage and impairment of spatial memory in KA-induced TLE mice. MicroRNA-23a can also regulate ADAM10, which contributes to epileptogenesis in pilocarpine-induced SE mice.	(Zhu et al., 2019a; Zhu et al., 2019b)

MicroRNAs	**Expression**	**Mechanisms**	**References**
MicroRNA-25-3p	Downregulation (KA, Mg^{2+} -free medium)	MicroRNA-25-3p targets OXSR1 to suppress oxidative stress and apoptosis of neurons, thereby suppressing epileptiform discharges in KA-induced epilepsy mice model and Mg^{2+} -free medium treated epilepsy cell model.	(Li et al., 2020)
MicroRNA-27a-3p	Upregulation (KA)	MicroRNA-27a-3p regulates ion channel-related DEGs in multiple mTLE and downregulation of microRNA-27a-3p inhibits apoptosis of hippocampal neurons and inflammatory response by upregulating MAP2K4 in KA-induced epilepsy models.	(Lu et al., 2019; Su et al., 2022b)
MicroRNA-29a	Downregulation (Mg^{2+}-free medium)	MicroRNA-29a regulates seizure-induced cell death and inflammation in Mg^{2+}-free medium treated epilepsy cell model.	(Wu et al., 2021)

MicroRNAs	**Expression**	**Mechanisms**	**References**
MicroRNA-34	Downregulation (KA, PTZ, Mg^{2+}-free medium, epilepsy patients, TSC)	Activated microRNA-34a may lead to impaired corticogenesis in TSC during early brain development and inhibition of microRNA-34a can regulate apoptosis and Notch signaling to inhibit epileptiform discharges in Mg^{2+}-free medium treated epilepsy cell model. MicroRNA-34c plays a negative role in seizure and cognitive function by regulating NMDARs and AMPARs in PTZ-induced epilepsy rat model. Decreased microRNA-34c-5p enhances neuroinflammation to increase loss of hippocampal neuron in DRE from KA-induced epilepsy mice model and in children with DRE.	(Huang et al., 2018; Wang et al., 2019a; Fu et al., 2020; Korotkov et al., 2021)
MicroRNA-101a-3p	Downregulation (pilocarpine, Mg^{2+} -free medium)	MicroRNA-101a-3p inhibits apoptosis and autophagy by downregulating c-FOS in pilocarpine-induced epilepsy rat model and Mg^{2+}-free medium treated TLE cell model.	(Geng et al., 2021)
MicroRNA-103a	Upregulation (pilocarpine)	Inhibition of microRNA-103a regulates BDNF to improve neuron injury and inhibit activated astrocytes in pilocarpine-induced epilepsy rat model.	(Zheng et al., 2019)

MicroRNAs	Expression	Mechanisms	References
MicroRNA-124	Downregulation (pilocarpine, PTZ)	MicroRNA-124 inhibits some target genes to prevent upregulation of hippocampal NRSF, which participates in epilepsy and promotes the activation of hippocampal microglia and inflammatory cytokines. MicroRNA-124 suppresses seizure, regulates CREB1 activity, and inhibits neuronal firing with decreased expression of NMDAR in pilocarpine and PTZ-induced epilepsy rat model.	(McClelland et al., 2014; Brennan et al., 2016; Wang et al., 2016c)
MicroRNA-125a-5p	Downregulation (PTZ)	MicroRNA-125a-5p targets CaMK4 to alleviate dysfunction and inflammation in PTZ-induced epilepsy rat model.	(Liu et al., 2019b)
MicroRNA-128	Downregulation (epilepsy patients, glioma-associated epilepsy) / Upregulation (KA, pilocarpine)	microRNA-128 is upregulated in KA-induced epilepsy rat model and promotes apoptosis by the SIRT1 cascade in PC12 cells. MicroRNA-128 can inhibit the expression of various ion channels and the signaling of ERK2 network that regulate neuronal excitability. MicroRNA-128 also inhibits SNAP-25 and SYT1 expression to regulate epilepsy sensitivity in KA-induced epilepsy mice model.	(Tan et al., 2013; Alsharafi and Xiao, 2015; Chen et al., 2019; Wang et al., 2021b).

MicroRNAs	Expression	Mechanisms	References
MicroRNA-129	Downregulation (KA, epilepsy patients)	Inhibition of microRNA-129-2-3p regulates GABRA1 to protect against refractory TLE in KA-treated primary hippocampal neurons and KA-induced epilepsy rat model. MicroRNA-129-5p also targets HMGB1 to inhibit the development of autoimmune encephalomyelitis-related epilepsy by TLR4/NF-kB pathway.	(Liu et al., 2017a; Wang et al., 2021a)
MicroRNA-132	Upregulation (KA, Mg^{2+}-free medium)	Depletion of microRNA-132 can reduce seizure-induced neuronal death in KA-induced epilepsy mice models and microRNA-132 can suppress BDNF/TrkB signaling to aggravate epileptiform discharges in the Mg^{2+}-free treated hippocampal neuronal model of SE. MicroRNA-132 also reduces the expression of pro-epileptogenic factors (COX-2, IL-1β, TGF-β2, CCL2 and MMP3) in human cultured astrocytes of TLE.	(Jimenez-Mateos et al., 2011; Xiang et al., 2015; Korotkov et al., 2020)

MicroRNAs	**Expression**	**Mechanisms**	**References**
MicroRNA-134	Upregulation (KA, pilocarpine, Mg^{2+}-free medium, epilepsy patients)	Inhibition of microRNA-134 can effectively reduce the occurrence of spontaneous recurrent seizures and silencing microRNA-134 can produce neuroprotective, reducing the severity of seizures in KA-induced epilepsy mice model. MicroRNA-134 inhibits the expression of CREB and p-CREB to regulate synaptic plasticity in pilocarpine-induced epilepsy rat model.	(Jimenez-Mateos et al., 2012; Zhu et al., 2015; Morris et al., 2019)
MicroRNA-135a	Upregulation (KA, epilepsy patients)	Antagonizing microRNA-135a can reduce spontaneous recurrent seizures to affect synaptic function and plasticity by targeting Mef2a in KA-induced epilepsy mice model. Inhibition of microRNA-135a protects glial cells against apoptosis by regulating SIRT1-related signaling pathway in KA-induced BV2 microglia epilepsy model.	(Vangoor et al., 2019; Wang et al., 2021c)
MicroRNA-136	Downregulation (pilocarpine)	MicroRNA-136 inhibits WNT/-Catenin signaling pathway to play a neuroprotective effect on pilocarpine-induced TLE rats.	(Cui and Zhang, 2022)

MicroRNAs	Expression	Mechanisms	References
MicroRNA-137	Downregulation (PTZ, pilocarpine, Mg^{2+}-free medium)	Overexpression of microRNA-137 inhibits seizure activity in two different epilepsy mouse models (PTZ and pilocarpine) and suppresses neuronal excitability in Mg^{2+}-free-induced brain slice model of epileptiform activity.	(Wang et al., 2018b)
MicroRNA-139-5P	Downregulation (pilocarpine, electrical kindling, epilepsy patients)	MicroRNA-139-5p negatively regulates GluN2A-NMDAR in pilocarpine-induced epilepsy rat model and TLE patients and upregulated microRNA-139-5p also regulates the Notch pathway to reduce spontaneous recurrent epileptiform discharge-induced apoptosis and oxidative stress in rat primary hippocampal neurons.	(Alsharafi et al., 2016; Zhao et al., 2021)
MicroRNA-141	Upregulation (KA)	Inhibition of microRNA-141 can inhibit P53 to protect against apoptosis by SIRT1 expression in KA-induced epilepsy rat model.	(Liu et al., 2019a)
MicroRNA-142	Upregulation (pilocarpine, epilepsy patients)	MicroRNA-142 performs well in differentiating between drug-resistant and drug-sensitive TLE. Inhibition of microRNA-142 promotes mitochondrial autophagy and reduces hippocampal neuron damage by targeting PINK1 in pilocarpine-induced epilepsy rat model.	(De Benedittis et al., 2021; Xiao et al., 2021)

MicroRNAs	**Expression**	**Mechanisms**	**References**
MicroRNA-145	Upregulation (pilocarpine, epilepsy patients)	Downregulation of microRNA-145 improves the abilities of learning and memory by reducing apoptosis of hippocampal neurons in pilocarpine-induced epilepsy rat model.	(Zhao et al., 2019a)
MicroRNA-146a	Upregulation (KA, pilocarpine, epilepsy patients, TSC)	MicroRNA-146a is a powerful regulator of microglia-mediated inflammation in the chronic TLE. MicroRNA-146a-CFH-IL-1β loop circuit mediates the perpetuate inflammation of chronic TLE in KA-induced epilepsy rat model and antagonists targeting microRNA-146a can protect against SE by regulating NF-κB pathway in pilocarpine-induced epilepsy rat model. MicroRNA-146a can ameliorate dysregulation of the MMP/TIMP proteolytic system in TSC.	(Aronica et al., 2010; Su et al., 2016; Li et al., 2018c; Zhang et al., 2018a; Broekaart et al., 2020)
MicroRNA-148a-3p	Upregulation (Mg^{2+} -free medium)	FS-related microRNA-148a-3p plays neuroprotective roles by increasing the proliferation of hippocampal neurons in Mg^{2+} -free medium treated epilepsy cell model.	(Yu et al., 2021)
MicroRNA-153	Downregulation (epilepsy patients)	MicroRNA-153 is downregulated in plasma and temporal cortex of mTLE patients and overexpression of microRNA-153 reduces HIF-1α expression in rat astrocytes of refractory epilepsy.	(Li et al., 2016)

MicroRNAs	Expression	Mechanisms	References
MicroRNA-155	Upregulation (KA, pilocarpine)	MicroRNA-155 contributes to epileptogenesis through the PI3K/Akt/mTOR signaling pathway. Inhibition of microRNA-155 attenuates MMP3 expression in cultured human astrocytes, increases the expression of BDNF and alleviates seizure severity in the pilocarpine-induced epilepsy, and attenuates KA-induced seizure by inhibiting microglia activation.	(Cai et al., 2016; Duan et al., 2018; Korotkov et al., 2018; Fu et al., 2019)
MicroRNA-181	Upregulation (KA, pilocarpine)	MicroRNA-181b can inhibit P38/JNK signaling pathway by targeting TLR4, thereby reducing apoptosis and autophagy in KA-induced epilepsy rat model. Inhibition of microRNA-181a-5p also activates SIRT1 to reduce neuronal apoptosis, neuroinflammation, oxidative stress, cognitive dysfunction and activation of astrocyte and microglia in pilocarpine-induced epilepsy rat model.	(Wang et al., 2019b; Kong et al., 2020)
MicroRNA-183	Upregulation (pilocarpine)	Downregulated microRNA-183 results in an inactivation of JAK/STAT signaling pathway by targeting Foxp1 to promote neuron proliferation and inhibit apoptosis of hippocampal neurons, thereby attenuating hippocampal neuron injury in pilocarpine-induced epilepsy rat model.	(Feng et al., 2019)

MicroRNAs	**Expression**	**Mechanisms**	**References**
McroiRNA-187-3p	Upregulation (electrical kindling)	MicroRNA-187-3p is upregulated and regulates KCNK10/TREK-2 potassium channel in electrical stimulation-induced SE.	(Haenisch et al., 2016)
MicroRNA-194-5p	Upregulation (Mg^{2+} -free medium, epilepsy patients)	MicroRNA-194-5p regulates the proliferation and apoptosis of hippocampus neuron in children with TLE and Mg^{2+} -free medium treated TLE cell model.	(Niu et al., 2021)
MicroRNA-199a-5p	Upregulation (pilocarpine)	Targeting of microRNA-199a-5p protects against neuron damage by SIRT1-p53 cascade in pilocarpine-induced epilepsy rat model.	(Wang et al., 2016a)
MicroRNA-200c-3p	Upregulation (pilocarpine)	Downregulation of microRNA-200c-3p upregulates RECK and inactivates the AKT signaling to decrease apoptosis of hippocampal neuron in pilocarpine-induced epilepsy rat model.	(Du et al., 2019)
MicroRNA-203	Upregulation (KA, pilocarpine, epilepsy patients)	MicroRNA-203 is targeted to Ppp2ca in both humans and mice, which can target Ppp2ca to increase seizure activity in the KA-induced SE model. And microRNA-203 antagomirs can targets GLRB to decrease the frequency of spontaneous seizures in pilocarpine-induced mice epilepsy.	(Lee et al., 2017; Zhang et al., 2018b)

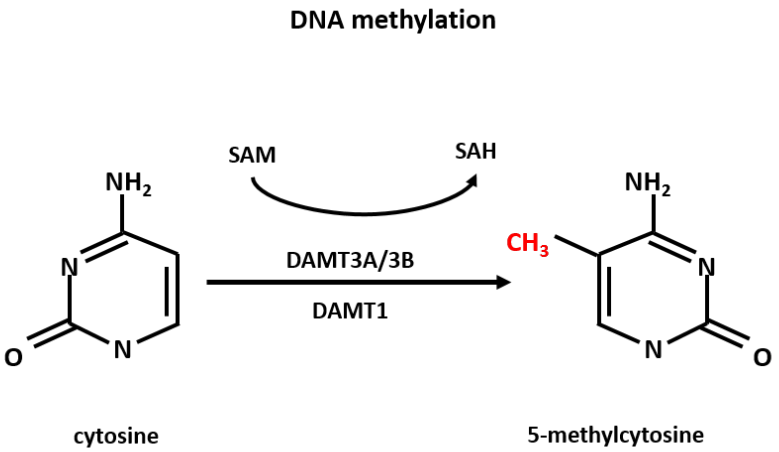
MicroRNAs	**Expression**	**Mechanisms**	**References**
MicroRNA-204	Downregulation (Mg^{2+}-free medium)	MicroRNA-204 regulates TrkB-ERK1/2-CREB signaling to inhibit epileptiform discharges in Mg^{2+}-free medium cultured hippocampal neurons.	(Xiang et al., 2016)
MicroRNA-211	Downregulation	Dynamic changes of microRNA-211 expression is associated with epileptiform activity and cholinergic imbalances in murine forebrain.	(Bekenstein et al., 2017)
MicroRNA-219	Upregulation (KA, epilepsy patients)	MicroRNA-219 regulates NMDARs in the amygdala and hippocampus of patients with mTLE and also suppresses seizure formation by regulating the CaMKII/NMDAR pathway in KA-induced epilepsy mice model.	(Zheng et al., 2016; Hamamoto et al., 2020)
MicroRNA-221-3p	Downregulation (KA)	MicroRNA-221-3p inhibits HIF-1α to suppress seizures and microglia activation in the VPA-resistant epilepsy of KA-induced epilepsy mice model.	(Fu et al., 2021)
MicroRNA-223	Upregulation (KA, epilepsy patients)	MicroRNA-223 also have the good performance in distinguishing drug-sensitive and drug-resistant TLE and microRNA-223 affects microglial autophagy by targeting ATG16L1 in KA-induced epilepsy mice model.	(De Benedittis et al., 2021; He et al., 2021b)
MicroRNA-322-5p	Downregulation (pilocarpine)	MicroRNA-322-5p regulates the TLR4/TRAF6/NF-ϰB axis to reduce neuronal inflammation in pilocarpine-induced epilepsy rat model.	(Zhou et al., 2022)

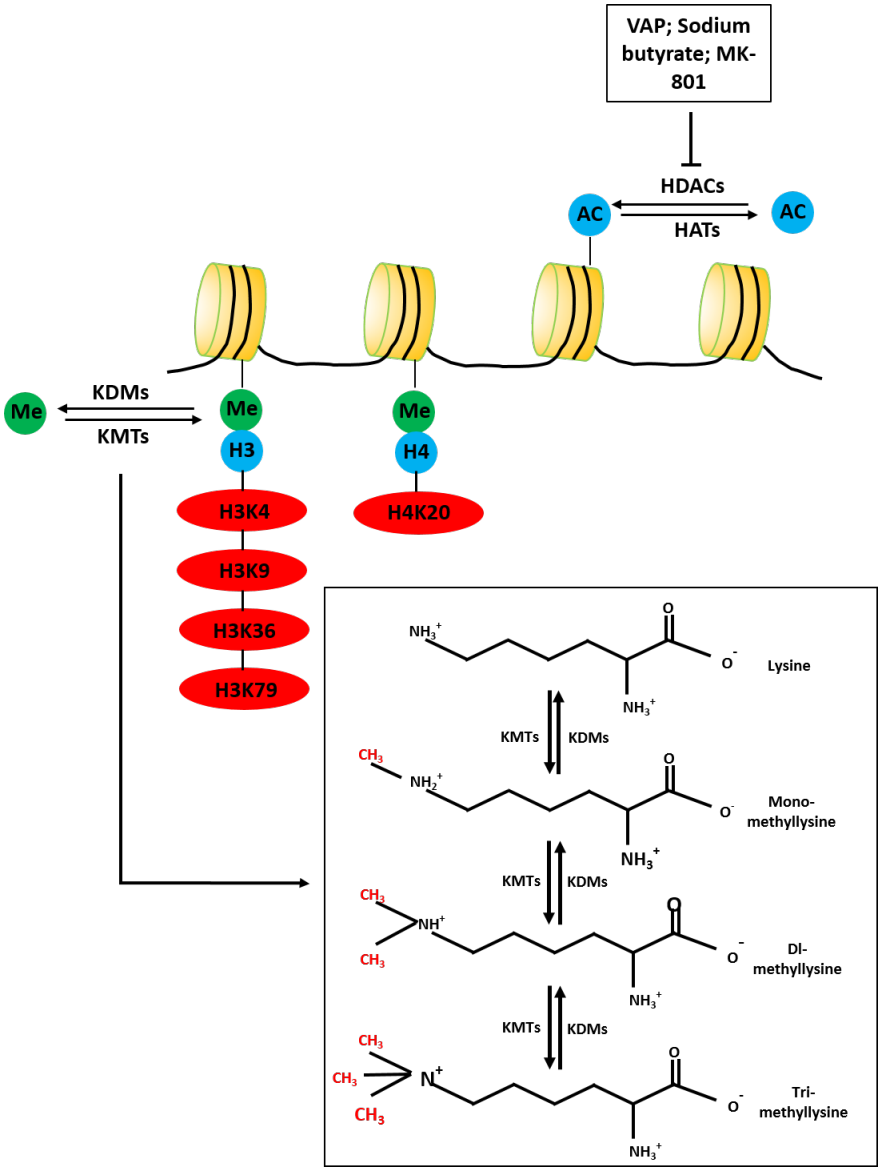
MicroRNAs	Expression	Mechanisms	References
MicroRNA-344a	Downregulation (PTZ)	MicroRNA-344a regulates seizure-induced apoptosis signaling pathways in PTZ-induced chronic epilepsy rat model.	(Liu et al., 2017b)
MicroRNA-451	Upregulation (KA)	MicroRNA-451 regulates GDNF expression to aggravate hippocampal neuronal apoptosis and seizure in KA-induced epilepsy mice model	(Weng et al., 2020)
MicroRNA-494	Downregulation (pilocarpine)	Overexpressed microRNA-494 inactivates the NF-κB signaling pathway to reduce hippocampal neuron injury by inhibiting RIPK1 in pilocarpine-induced epilepsy rat model.	(Qi et al., 2020)
MicroRNA-542-3p	Downregulation (KA)	MicroRNA-542-3p suppresses TLR4/NF-κB signaling pathway to reduce seizure-induced brain injury and the expression of P-gp in KA-treated primary hippocampal neurons and KA-induced epilepsy rat model.	(Yan et al., 2019)

Table2. Regulation of lncRNAs and circRNAs in epilepsy.

LncRNAs	Mechanisms
BDNF-AS	Concerning epilepsy, a study found that the expression of BDNF is upregulated in human neocortex r
LncRNA H19	LncRNA H19 suppresses microRMA-let-7b to regulate hippocampal neuron apoptosis and lncRNA H
LncRNA FTX	LncRNA FTX regulates microRNA-21-5p/SOX7 axis to suppress apoptosis of hippocampal neurons i
LncRNA UCA1	LncRNA UCA1 regulates microRNA-495/Nrf2-ARE signal pathway to suppress seizure-induced brain
LncRNA MALAT1	Down-regulation of LncRNA MALAT1 protects hippocampal neurons against excessive autophagy an
LncRNA PVT1	Silencing lncRNA PVT1 can downregulate WNT signaling pathway to promote the expression of BDI
LncRNA ILF3-AS1	LncRNA ILF3-AS1 suppresses microRNA-212 to mediate epileptogenesis in the hippocampus and tar
LncRNA ZFAS1	LncRNA ZFAS1 upregulates microRNA-421 to activate the PI3K/AKT pathway, thereby inhibiting a
LncRNA MALAT1	LncRNA MALAT1 regulates dendritic spine density. Downregulated lncRNA MALAT1 regulates the
LncRNA BC1	Loss the lncRNA BC1 reduced convulsive thresholds.
LncRNA KCNH5-1	LncRNA KCNH5-1 plays a key vital role in developing TLE with Hippocampal Sclerosis (HS).
LncRNA NEAT1	LncRNA NEAT1 is responsive to neuronal activity and is associated with hyperexcitability states. Ln
LncRNA GAS5	LncRNA GAS5 inhibits microRNA-219 to affect CaMKIIγ/NMDAR pathway and promote the progre
LncRNA TUG1	LncRNA TUG1 may be a biomarker of TLE diagnosis in children, and regulates miR-199a-3p to affec

LncRNAs	Mechanisms
LncRNA XIST	LncRNA XIST sponges miR-29c-3p and regulates NFAT5 expression to promote the secretion of infla
LncRNA Nespas	LncRNA Nespas, as a regulator of microRNA-615-3p, inhibits the PI3K/Akt/mTOR pathway to supp
LncRNA SNHG1	SP1 activated-lncRNA SNHG1 regulates microRNA-154-5p/TLR5 axis to mediate the development o
Circ-EFCAB2	Circ-EFCAB2 may be potential therapeutic targets and biomarkers for TLE patients.
Circ-UBQLN1	Circ-UBQLN1 upregulates microRNA-155-mediated SOX7, thereby inhibiting apoptosis and oxidative
Circ-DROSHA	Circ-DROSHA may be potential therapeutic targets and biomarkers for TLE patients. Circ-DROSHA
Circ-ANKMY2	Circ-ANKMY2 regulates the microRNA-106b-5p/FOXP1 axis to affect TLE progression.
Circ-Hivep2	Circ-Hivep2 regulates microRNA-181a-5p/SOCS2 signaling to promote microglia activation and inflar





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