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# MicroRNAs dysregulation in epilepsy

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ABSTRACT

Epilepsy is a syndrome characterized by recurrent spontaneous seizures due to neuronal hyperactivity in the brain. MicroRNAs (miRNAs) are small, non-coding RNAs that regulate post-transcriptional expression of protein-coding mRNAs, which may have key roles in the pathogenesis of neurological disorders. Evidence indicates that miRNAs are emerging as a critical new layer of gene expression regulation with implications for the cause and treatment of epilepsy. Accumulating studies in epilepsy suggest that numerous specific miRNAs are dysregulated. Recent studies have explored several target genes and pathways of miRNAs in order to find out therapeutic approaches to epilepsy. Here, we review current findings regarding miRNA research in humans and animal models to provide a solid foundation for further research aiming at understanding the potential contribution of miRNAs to epilepsy pathophysiology.

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## 1. Introduction

MicroRNAs (miRNAs) belong to a family of non-coding small RNAs and regulate gene expression through inhibition of translation levels or fracture targeted mRNAs. MiRNAs play a vital role as environmental biosensors via regulating the expression of gene and evolving functional gene networks (Schratt, 2009). Increasing evidence highlights the function of miRNAs participating in the underlying molecular mechanism in neurological diseases. In addition, miRNAs are evaluated to apply to clinic as biomarkers for neurological diseases (de Planell-Saguer and Rodicio, 2011). A number of studies have investigated the role of miRNAs in epilepsy. Both acute neurological insults and prolonged seizures can regulate miRNA expression in brain (Aronica et al., 2010; Hu et al., 2011). In response to brain injury after seizures, several miRNAs altered (Liu et al., 2009b). Several miRNAs have been found to be differentially expressed in the hippocampus of temporal lobe epilepsy (TLE) or status epilepticus (SE) models. The expression and functional changes of inflammation-, development-, pro-apoptotic and neuronal death-associated miRNAs in epilepsy have been identified.

Epilepsy, a disorder of recurrent unprovoked seizures, has a lifetime prevalence of ~0.5% affecting almost 50 million people worldwide. The characteristics of epilepsy include several factors: the alterations in genetic and environmental factors and a series of abnormal epigenetic factors and processes (Qureshi and Mehler, 2010). Epileptogenesis is associated with several factors, including complex temporal and spatial abnormalities of neural network structure, activity

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mediated by posttranslational modifications of proteins, activation of immediate early genes (IEGs), other alterations in profiles of gene expression and function (e.g., GABAA receptor subunit, CREB, JAK-STAT, BDNF, and EGR3). These factors eventually lead to deregulated neural circuits with a predisposition for synchronous electrical activity (Rakhade and Jensen, 2009). Focal epilepsies result in seizures beginning in a localized fashion, which then spread by recruitment of other brain areas due to focal pathological changes. Therefore, the occurrence of epileptic activity is probably caused by greater spread and neuronal recruitment secondary to a combination of enhanced connectivity and excitatory transmission (Duncan et al., 2006). TLE is the most common syndrome in adults and is thought to involve neuronal death or dysfunction, changes to ion channel function, gliosis, neuroinflammation and neurogenesis (McNamara et al., 2006; Pitkänen and Lukasiuk, 2011). Emerging evidence shows that epilepsy and epileptogenesis are controlled by epigenetic factors and gene products that regulate multiple genes and proteins on a system level (Kobow and Blümcke, 2011; Lubin, 2012). Epilepsy research has focused on the question that whether miRNA are altered by seizures during epileptogenesis or in chronic epilepsy. Understanding how the expressions of related genes are regulated could thus provide valuable insights into the molecular basis of epilepsy and illuminate the path toward novel therapeutic avenues. Besides, the McKiernan et al. study showed that loss of Dicer and failure of mature miRNA expression might be a characteristic of the pathophysiology of hippocampal sclerosis (HS) in patients with TLE.

As key factors in biological processes, several miRNAs have been found in human brains (Lindsay, 2008; Pauley et al., 2009; Sonkoly et al., 2008). Here, we review current findings regarding miRNA research in humans and animal models to provide a solid foundation for further research aiming at understanding the potential contribution of miRNAs to epilepsy pathophysiology.

## 2. Biology of miRNAs

MiRNAs are small endogenous non-coding RNA molecules consisted of 21–23 nucleotides. MiRNA is one of the small RNA (siRNA, miRNA and piRNA) species and interactive Argonaute/Piwi protein members of the protein family, and function as the core of a group of different complex known as the RNA-induced silencing complex (RISC) (Jinek and Doudna, 2008). These small miRNAs generally target one or more mRNAs and regulate gene expression through inhibition of translation levels or fracture targeted mRNAs. MiRNAs could also enhance mRNA translation and induce gene expression as a positive regulator via binding to target gene promoter (Huang et al., 2010; Place et al., 2008; Vasudevan et al., 2007; Verdel et al., 2009). MiRNAs add more complexity to their originally described mode of action. MiRNAs regulate most mRNA (Friedman et al., 2009) as to affect many aspects of the development of animals and plants (Friedman and Avraham, 2009), including many aspects of brain function (Chandrasekar and Dreyer, 2009; Edbauer et al., 2010; Hansen et al., 2010; Konopka et al., 2010). Moreover, miRNAs often turn to be dysregulated in cancer and other disorders (Kocerha et al., 2009; Medina and Slack, 2008). In the intervening years, studies have identified over 700 miRNAs in mice and approximate 1500 in humans. Different types of small RNA molecules are related to the evolution and function. For instance, many annotated miRNA precursors possess box H/ACA snoRNA features (Scott et al., 2009) and other miRNAs have a nucleolar location (Politz et al., 2009). Further research is still needed to study the biological mechanism and function of miRNAs, including the identification of the parameters of the target recognition (Didiano and Hobert, 2006; Didiano and Hobert, 2008; Grimson et al., 2007; Shin et al., 2010) especially in the views of the developmental regulation of miRNA subtypes. About one-third of the genes are situated within the protein-coding mRNAs, while the other two-thirds of the miRNA genes are intergenic (Delay et al., 2012). MiRNA contains the seed sequence (nucleotides 2–8), majority of which may target the same genes. Moreover, one single miRNA can target up to hundreds of genes and adjust a plurality of biological pathways (Baek et al., 2008; Selbach et al., 2008). MiRNAs regulate expression of critical epigenetic regulators including DNMTs, polycomb group proteins, HDACs and MeCP2 (Sato et al., 2011). Related researches show that miRNAs play a universal role in modulating the expression of target genes in neurons (Hwang et al., 2012). As miRNAs regulate mRNA translation locally in the synaptodendritic compartment in an activity-dependent way, the spatial specificity of gene expression was realized (Hwang et al., 2012). Of which some expressed in specific neuroanatomical regions, subcellular compartments or cell types playing special role in developmental programs and brain homeostasis as well (Cao et al., 2006; Mercer et al., 2008). The altered expression of miRNAs in SE demonstrates that regulation of miRNAs translation may contribute to changes in protein expression during epileptogenesis. Recent discovery of an episode of SE leading to a reduction in synaptoneurosome miRNAs indicates that SE may damage the ability of synapses to respond to normal activity cues (Risbud and Porter, 2013). The Pichardo-Casas et al. (2012) study has demonstrated that the dynamic modulation in the local distribution of miRNAs from brain might contribute to controlling localized protein synthesis at the synapse.

MiRNA biogenesis is a tightly regulated multi-step process (Fig. 1). It was the first molecule transcribed into longer primary miRNA (pri-miRNA) that subsequently form mature 22 nucleotide molecules. The process is followed by many steps: firstly, a primary miRNA transcript, mediated mainly by RNA polymerase II (Pol-II), is produced and called pri-miRNA (Tan et al., 2013). Then, a series of nuclear enzymes cleave the primary miRNA transcripts to 70–100 nucleotides precursor miRNA (miRNA precursor) hairpin. Finally, a second cleavage occurs in the cytoplasm. Mature double-stranded RNAs of 22 nucleotides in length are achieved with the help of RNAase III enzyme Dicer, loss of which will cause neuronal and glial dysfunction, seizures, and neurodegeneration. MiRNA genes are interspersed throughout the genome and following transcription. The drosha complex cleaves pri-miRNA to a pre-miRNA. Finally, a Dicer containing complex cleaves it to the mature miRNAs. Recent study (McKiernan et al., 2012) has shown that the Dicer protein expression levels are significantly lower in certain TLE patients with HS, which implies loss of Dicer, and failure of mature miRNA expression may be a feature of the pathophysiology of HS in patients with TLE.