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Study on MiRNA Epigenetic Intervention for Epilepsy

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Abstract

MiRNAs are a family of small non-coding RNAs that control levels of multiple proteins by post-transcriptionally decreasing messenger RNA stability and translation. MiRNA is a part of the epigenetic machinery. In addition to post-transcriptional gene silencing by miRNAs, the epigenetic mechanisms also include DNA methylation, histone modifications and their crosstalk. Epigenetic modifications were reported to play an important role in many disease onsets and progressions and can be used to explain several features of epilepsy. However, miRNA not only function as a part of epigenetic machinery, but are also epigenetically modified by DNA methylation and histone modification like any other protein-coding gene. There is a strong connection between epigenetic and MiRNA, and any dysregulation of this complex system can result in various physiological and pathological conditions. Currently, there is an unmet need for antiepileptic drugs that truly prevent the development of epilepsy in high-risk populations. New findings in animal models and human brain tissue suggest that microRNAs play a crucial role in epileptogenesis and the pathophysiology of chronic epilepsy. **Objectives:** This paper focuses on the epigenetic role of miRNA in the development of epilepsy and potential targets for drug therapy. **Methods:** In this paper, through the keywords epilepsy, epigenetic, methylation, miRNA, non-coding RNA search in PubMed, SPIS, GeenMedical, Google Scholar and Web of Science, to study the potential application of miRNA epigenetic regulation in the treatment of epilepsy. **Results:** Future treatments that manipulate miRNA epigenetic processes, such as Anti-oligonucleotides, DNA methylation and Nucleic Acid Aptamers, to treat or prevent epilepsy. **Conclusion:** Overall, miRNA epigenetic drugs have become a new frontier target to achieve a cure for epilepsy.

Keywords

MiRNA Epigenetic, Epilepsy, Treatment

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1. Introduction

Epilepsy is a clinical syndrome of highly synchronous abnormal discharge of brain neurons caused by many causes. About 65 million people worldwide suffer from epilepsy which is a common nervous system disease. The occurrence of epileptic diseases will not only cause health problems, but also have a serious impact on patients' mood, occupation, life and overall quality of life. Epilepsy patients have a large psychological pressure and are often associated with various mental disorders, and at present the treatment of epilepsy is usually with drugs, long-term use of difficult to adhere to, and larger side effects, patient compliance is poor, so looking for a new potential therapeutic target is very important. MiRNA can not only by reducing the transcription of mRNA stability and translation to control the level of a variety of proteins, but also part of the epigenetic mechanisms can through DNA methylation and histone modification methods to regulate a range of important steps in gene expression, including RNA transcription, translation, and expression of key epigenetic enzymes [1] [2] [3]. MiRNA epigenetic may represent an important regulatory mechanism and therapeutic target for epilepsy. This multi-target property has a distinct advantage for the disease change of epilepsy because it provides the possibility of interrupting several processes simultaneously. However, it also increases the possibility of unnecessary or unexpected side effects from any treatment based on MiRNA epigenetics.

2. Epilepsy Overview

2.1. Molecular Cascades of Epilepsy

Epilepsy is the result of abnormal synchronous discharge of thousands of neurons. The mechanism of epilepsy is not clear at present. A major hypothesis for the occurrence and development of epilepsy is that large-scale changes in gene transcription and protein expression lead to abnormal network remodeling and over excitation, leading to repeated epilepsy. Studies have shown that epigenetic mechanisms, including changes in post-translational DNA winding proteins, chemical modifications of DNA, and the activity of various non-coding RNA molecules have important effects on these gene networks in epilepsy. The progression of epilepsy can be divided into three stages: the initial injury stage, the latency stage and the chronic stage [4]. These signals induce changes that lead to neuro inflammation, oxidation, apoptosis, synaptic plasticity, and functional alterations in the neuronal and neurovascular unit [5]. The resulting physiological responses alter gene expression in neuronal ensembles by modifying the epigenetic landscape. Next, a dynamic process ensues leading to the rearrangement of synaptic circuitry, neuronal damage, neurogenesis, and synchronic hyperexcitability. These dynamic changes are characteristic of the latent phase, characterized as the most unpredictable phase because it can last several weeks, months, or even years without any clinical symptoms. These changes eventually manifest in spontaneous seizure activity, marking onset of the chronic phase. Intervening

in these underlying molecular cascades of epilepsy may lead to discoveries and eventual breakthroughs in the development of a cure for epilepsy. Temporal lobe epilepsy is the most common epilepsy syndrome in adults and is associated with large-scale, wide-ranging changes in gene expression in the hippocampus. Hippocampi from such patients can display hippocampal sclerosis, which is a histopathologic abnormality including segmental neuron loss as well as other changes. Drug-resistance and hyperexcitability of chronic epileptic brain can be explained by epigenetic changes to DNA, as DNA methylation is highly dynamic in the hippocampus. Miller-Delaney report genome-wide DNA methylation changes in human temporal lobe epilepsy with or without hippocampal sclerosis that may contribute to the molecular architecture of the epileptic brain. In addition, recent experimental studies from cell and animal models have shown that miRNA epigenetic regulation can promote epileptogenesis and affect neuronal hyperexcitability, which is associated with intellectual disability [6] [7] [8].

2.2. Epidemiology

According to statistics, epilepsy is one of the common diseases of the nervous system [9], and the annual incidence of epilepsy is (50 - 70)/100,000. The prevalence rate was about 5‰. The mortality rate was (1.3 - 3.6) per 100,000 people, 2 - 3 times that of the general population. At present, there are more than 9 million epilepsy patients in China, the annual new epilepsy patients 650,000 - 700,000, about 30% for refractory epilepsy, China refractory epilepsy patients at least in more than 2 million.

3. The MiRNA Epigenetic Signatures

MiRNA not only function as part of epigenetic mechanisms, but also epigenetic modifications to themselves through the same mechanisms as protein-coding genes. Its characteristic basically has the following respects. MiRNA can target specific epigenetic regulators, such as DNA methyltransferases and silencing transcription factors [10]. Some MiRNA can directly regulate their activity by targeting the promoter region of specific genes, and directly affect gene expression in the nucleus at the transcriptional level. One possible mechanism by which MiRNA regulates gene expression is to induce binding and activity of RNA polymerases in these specific genes. MiRNA can recruit other chromatin modifications, lead to transcriptional silencing, and play an epigenetic role as other epigenetic regulators or regulators of specific gene expression [11]. In addition, miRNA expression is also regulated through histone modifications, such as methylation and silencing of overexpression of transcription factors, which can activate or inhibit miRNA expression. More than 2500 miRNAs have been identified in humans, and each miRNAs can affect gene transcription at multiple sites of mRNA. MiRNAs are involved in a series of important steps in the regulation of gene expression, including transcription, translation and expression of key epigenetic enzymes.

4. MiRNA Epigenetic Mechanisms Implicated in Epilepsy

MiRNA not only participate in protein translation but also participate in the immune response during the regulation of epilepsy. MiRNA regulate gene translation in early brain development, which is critical for proper dendrite formation, synapse formation, and synapse maturation. MiRNA can regulate the translation of various proteins in neurons [12], for example, Mir-132 inhibits the expression of p250GAP in the morphological proteins of neurons [13] and the NMDA receptor subunit of the channel protein Mir-125b [14]. Epilepsy is associated with abnormal production of proteins. This includes significant transcriptional inhibition. The first report on miRNA expression response after epilepsy was completed by Nudelman and his colleagues [15]. They studied the expression of Mir-132 in the hippocampus, which is involved in dendrite growth and morphology. They found that seizures caused elevated levels of priMir-132 and mature Mir-132.

MiRNAs play an important role in immune response, and the immune system is increasingly prominent in the occurrence and maintenance of epilepsy [16]. Among them, TLR4 was upregulated after experimentally induced epilepsy in mice [17]. TLR4 levels are partly controlled by MiRNA, including Let-7i. The ligand of TLR4 appears to be HMGB1, which is thought to be released from damaged neurons to promote epileptic seizures [18]. Recently, TLRs have been identified as direct targets of miRNAs in the brain. The *in vivo* target of Mir-146a in epilepsy remains unclear, but *in vitro* studies have shown that Mir-146a inhibits the levels of inflammation-promoting proteins such as IRAK1/2 and TRAF6, as well as il-1B levels in the negative feedback loop [19].

In addition to the above mechanisms, MiRNA can recruit other chromatin modifications, lead to transcriptional silencing, and play an epigenetic role as other epigenetic regulators or regulators of specific gene expression. For example, MiRNA can recruit silencing transcription factors, which are epigenetic regulators also known as neuro suppressive silencing factors, whose function is to regulate DNA, histones and chromatin by recruiting a series of epigenetic inhibitors [20]. Through this mechanism, REST/NRSF is thought to control the expression of more than 1800 genes associated with synaptic transmission, synapse generation, excitability, and neurogenesis [21].

A growing body of evidence indicates that epilepsy and epilepsy by MiRNA epigenetic factors and gene product control, and epigenetic factors and gene product at the system level control to identify multiple genes and proteins in the epileptic brain samples increase of miRNAs epigenetic function directly, will help to better understand the complex mechanisms of epilepsy occurs [22].

5. Prospects for MiRNA Epigenetic Treatment for Epilepsy

5.1. The Application of Anti-Oligonucleotides

The main method of manipulating therapeutic MiRNA is the use of oligonucleotides that can lead to long-term effective reduction of miRNA levels [23]. Potas-

sium channels can be upregulated by targeting MiRNA bound to 3'UTR, that is, the injection of anti-oligonucleotides of targeted miRNA can increase the surface expression of potassium channels and reduce the neuro excitability, thus achieving the effect of anti-epilepsy [24].

Early functional studies have shown that the use of anti-oligonucleotides to silencing brain-specific Mir-134 [25], Mir-10a-5p, Mir-21A-5p and Mir-142A-5p [26] can effectively reduce epileptic status, epileptic damage and the late onset of epileptic seizures, and have a strong anti-epileptic effect.

Proteomics data, RNA sequencing, and path analysis of the prediction and validation targets of these MiRNA suggest that the transformed growth factor-signal is a common seizure correction mechanism. Correspondingly, the anti-epileptic effect of antiepileptic agents was blocked by the inhibition of transforming growth factor-signaling [27].

It is exciting that oligonucleotide therapies are now approved, such as Nusinersen for spinal muscular atrophy [28]. RNA therapy has been very effective in preclinical studies targeting MiRNAs. At present, more than ten different MiRNAs have been inhibited by this method, and the effect on induced or spontaneous epilepsy has been reported in some cases [29]. Several other studies have shown that the use of oligonucleotides to target synaptic development and post-seizure upregulated MiRNA improves epileptic or rodent susceptibility to epileptic seizures. Targeting Mir-129 and mirNA-132 with oligonucleotide can protect neurons from damage and reduce the severity of epileptic seizures before induced epileptic persistence in mice. Similarly, oligonucleotide administration of Mir-135a reduced spontaneous epileptic seizures in mice that had already developed epilepsy. Finally, oligonucleotide inhibition of Mir-203 also reduced spontaneous epileptic seizures. In summary, the use of oligonucleotide targeted MiRNA can be used as an antiepileptic intervention or as a substitute for traditional antiepileptic drugs in the treatment of refractory epilepsy.

5.2. The Application of DNA Methylation

Data have shown that there are pathologically specific differences in DNA methylation patterns in patients with epilepsy, and miRNA may be particularly sensitive to DNA methylation, thus providing valuable insights into the molecular mechanisms controlling gene expression in human epilepsy [27]. If a gene is epigenetic silenced due to DNA methylation, this method can be used to increase its expression, wiping out methylation markers that inhibit expression. For example, the RELN gene, Kobow and his colleagues found that when the RELN gene was highly methylated, the granular cells in the hippocampus dispersed. The CRISPR-based approach could in principle achieve promoter demethylation, which would help reduce pathologic granulocytic cell dispersion in patients with treatment-resistant epilepsy.

5.3. The Application of Nucleic Acid Aptamers

Nucleic acid aptamers are a new class of antiepileptic drugs with characteristics

of non-toxicity, specificity, regulation of ion channel permeability and inhibition of inflammatory proteins [28]. Specific ligands by non covalent, hydrogen bond, ionic bond and the van der Waals force interact with receptors, methyl ribonucleotide modification make the specific nucleic acid ligand nuclease resistance, and allow them to survive in the protein, because different receptors in the development of epilepsy in plays an important role, so the ligand can be used to inhibit or activate specific receptors, which can achieve the effect of antiepileptic. In addition, nucleic-acid specific ligands have a better tissue penetration capability than antibodies, making it possible to use nucleic-acid specific ligands for targeted administration of epilepsy across the blood-brain barrier.

6. Summary and Prospect

The present review of epigenetically regulated miRNAs further emphasizes the importance of the epigenetic network in pathogenesis of epilepsy. In summary, MiRNA epigenetic modulation is a powerful strategy for therapeutic intervention with the possibility of novel drugs that inhibit epigenetic enzymes critically involved in the progression of epileptogenesis. The emerging evidence reviewed in this article reveals the pharmacotherapeutic potential of targeting epigenetic pathways underlying the development of epilepsy. The next steps for research in the field should focus on how to identify epileptogenic disorders that would respond effectively to a particular epigenetic therapy. Modulating these pathways by altering or inhibiting select epigenetic agents can lead to the effective interruption of epileptogenesis and chronic epilepsy. Evidently, the framework for using epigenetic drugs, in combination or alone, may present a momentous opportunity for curing epilepsy [29].

Other forms of non-coding RNA are becoming key to gene expression control, and the recognition of these functions and ongoing research into miRNA epigenetics will change our understanding of disease mechanisms, as well as the future treatment of experimental and clinical epilepsy.

While there are challenges in delivering large molecules such as anti-oligonucleotide inhibitors or mimics to the patient's brain, the multi-target effects of MiRNA increase the additional risk of unexpected side effects. The potential genetic variation of miRNAs should be explored as candidate factors to alter disease susceptibility. These findings provide exciting advances and rich targets for the epigenetic regulation of miRNA, but challenges still remain before their role in the pathogenesis, diagnosis, and treatment of epilepsy can be translated into clinical applications.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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