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CIRCULATING MICRORNAS AS POTENTIAL BIOMARKERS IN THE DIAGNOSIS AND MANAGEMENT OF EPILEPSY

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ABSTRACT

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures, affecting millions of people globally. Despite advances in diagnostic tools, early detection and personalized treatment remain challenging. Recently, circulating microRNAs (miRNAs), small non-coding RNA molecules involved in gene regulation, have emerged as promising biomarkers for various forms of epilepsy. This article reviews the potential role of circulating miRNAs in epilepsy, focusing on their diagnostic, prognostic, and treatment-monitoring capabilities. Studies have identified specific miRNAs, such as miR-146a, miR-199a, and miR-134, that are differentially expressed in different epilepsy forms, including temporal lobe epilepsy, genetic epilepsies, drug-resistant epilepsy, and status epilepticus. These miRNAs are implicated in critical processes such as neuroinflammation, neuronal excitability, and synaptic plasticity. Technological advancements in miRNA detection, such as quantitative PCR and next-generation sequencing, have enabled the identification of miRNA profiles in blood, serum, and cerebrospinal fluid. While circulating miRNAs hold great potential for non-invasive monitoring of epilepsy, further research and validation are required to standardize detection methods and assess their clinical utility. Ultimately, miRNA-based biomarkers could improve the diagnosis, prognosis, and treatment of epilepsy, leading to more personalized and effective therapeutic strategies.

KEYWORDS

Circulating microRNAs, Epilepsy, Biomarkers, Seizures, Temporal Lobe Epilepsy, Genetic Epilepsies, Drug-Resistant Epilepsy, Status Epilepticus, miR-146a, miR-155, miR-199a, Non-Invasive Diagnostics, miRNA Detection.

INTRODUCTION

Epilepsy is one of the most common neurological disorders worldwide, affecting around 50 million people, with approximately 30% of patients experiencing drug-resistant epilepsy (DRE). This chronic condition is characterized by recurrent, unprovoked seizures, resulting from abnormal electrical activity in the brain. Epilepsy is not only a debilitating disorder for patients but also poses a significant public health burden due to its high prevalence, impact on quality of life, and the substantial healthcare costs associated with diagnosis, treatment, and management. Despite advances in pharmacological treatments and surgical interventions, the management of epilepsy remains suboptimal, particularly in cases of drug-resistant epilepsy.

The complexity of epilepsy stems from its heterogeneity in terms of etiology, clinical manifestation, and underlying pathophysiology. It can result from genetic factors, brain injury, infections, or developmental malformations, and present with various seizure types. Diagnosing epilepsy and determining its etiology often rely on clinical evaluation, electroencephalography (EEG), and imaging techniques, such as magnetic resonance imaging (MRI). However, these tools are not always definitive and often fail to identify the specific molecular mechanisms underlying the disorder, which can limit the ability to tailor treatments effectively. This limitation is particularly concerning for patients with drug-resistant epilepsy, for whom treatment options are severely restricted.

Given the challenges associated with traditional diagnostic and therapeutic approaches, there is a growing interest in the identification of novel biomarkers that can provide additional insights into the molecular underpinnings of epilepsy. Among the most promising candidates are microRNAs (miRNAs), small, non-coding RNA molecules that regulate gene expression post-transcriptionally. miRNAs influence various cellular processes, including neuronal development, synaptic plasticity, neuroinflammation, and apoptosis, all of which are implicated in the pathophysiology of epilepsy. Additionally, miRNAs are stable in peripheral blood, cerebrospinal fluid (CSF), and other body fluids, making them ideal candidates for non-invasive diagnostic and prognostic biomarkers.

What are microRNAs?

MicroRNAs are short, approximately 22 nucleotides long, single-stranded RNA molecules that regulate gene expression at the post-transcriptional level. They exert their effects by binding to the 3' untranslated region (UTR) of target messenger RNAs (mRNAs), leading to either mRNA degradation or inhibition of translation. Through this mechanism, miRNAs play a crucial role in regulating a variety of cellular processes, including cell differentiation, proliferation, apoptosis, and synaptic plasticity.

The role of miRNAs in the brain is particularly significant. The central nervous system (CNS) has a highly dynamic miRNA expression profile that is involved in the regulation of neural development, neuronal differentiation, and synaptic activity. miRNAs are also critical in maintaining the balance between excitation and inhibition within the brain, a process that is disrupted in epilepsy. Their ability to modulate neuronal excitability and synaptic plasticity positions miRNAs as central regulators in the development of epileptogenesis—the process through which normal brain tissue becomes susceptible to seizure activity.

The Role of miRNAs in Epilepsy

Epileptogenesis is a complex, multifactorial process that involves alterations in neurotransmitter systems, ion channels, neuroinflammation, and synaptic plasticity. Dysregulated gene expression is a key feature of epileptic brains, and miRNAs are among the most important regulators of gene expression in neurons. Studies have shown that specific miRNAs are differentially expressed in the brains of individuals with epilepsy, suggesting that they may play a critical role in both the development of seizures and the progression of the disease.

Several mechanisms by which miRNAs contribute to epilepsy have been identified:

1. Neuroinflammation: Chronic neuroinflammation is a hallmark of epilepsy, and miRNAs play a central role in modulating the inflammatory response in the brain. MiRNAs such as miR-146a and miR-155 are upregulated in response to inflammation and have been implicated in the regulation of inflammatory cytokines. Dysregulation of these miRNAs may contribute to the development of seizures by promoting neuroinflammation, which in turn alters neuronal excitability.

2. Neuronal Excitability and Synaptic Plasticity: miRNAs such as miR-134, miR-132, and miR-29 have been shown to regulate neuronal excitability and synaptic plasticity, both of which are critical in the initiation and propagation of seizures. By modulating the expression of ion channels and neurotransmitter receptors, miRNAs can influence the threshold for seizure activity. For example, miR-132 has been found to regulate dendritic growth and synaptic plasticity, making it a key player in the response of neurons to injury and epileptogenesis.

3. Ion Channel Regulation: Epilepsy is often associated with dysfunction in ion channels, which are critical for maintaining neuronal activity and synaptic communication. miRNAs, such as miR-181a, are involved in the regulation of ion channel expression. Disruptions in miRNA-mediated ion channel regulation can lead to hyperexcitability and the development of seizures.

4. Neurogenesis and Cell Death: miRNAs also participate in regulating neurogenesis and apoptosis in the brain. miR-124, for example, is involved in neuronal differentiation and survival. Dysregulated expression of miR-124 in epilepsy has been associated with impaired neurogenesis and increased neuronal death, which can exacerbate the progression of the disease.

5. Epigenetic Modifications: Epilepsy can also be associated with epigenetic changes, including alterations in DNA methylation and histone modifications. miRNAs are known to interact with epigenetic regulators, and their dysregulation can contribute to the development and progression of epilepsy by altering gene expression patterns that control neuronal plasticity and function.

Circulating miRNAs as Biomarkers for Epilepsy

The use of circulating miRNAs as biomarkers for epilepsy holds significant promise due to their stability in body fluids such as blood, serum, and cerebrospinal fluid. Circulating miRNAs are protected from degradation by extracellular vesicles (e.g., exosomes) or RNA-binding proteins, which allow them to circulate freely in the bloodstream and other bodily fluids. This stability makes them ideal candidates for non-invasive diagnostic and prognostic tests.

The potential of circulating miRNAs in epilepsy is being explored for several purposes:

1. Early Diagnosis: miRNAs could serve as early biomarkers for epilepsy, potentially allowing for quicker diagnosis in individuals who may not yet exhibit obvious clinical signs of the disease. For example, miR-146a has been shown to be upregulated in the serum of patients with temporal lobe epilepsy, suggesting that it could serve as an early indicator of epileptic activity.

2. Differentiating Epilepsy Subtypes: The diverse forms of epilepsy, such as temporal lobe epilepsy, generalized epilepsy, and drug-resistant epilepsy, may be associated with distinct miRNA profiles. Identifying specific miRNAs that are differentially expressed in these forms could help differentiate between various types of epilepsy and improve personalized treatment strategies.

3. Monitoring Disease Progression: miRNA expression levels can change in response to disease progression, making them useful for monitoring the course of epilepsy. For instance, miR-199a is elevated in patients with drug-resistant epilepsy, and monitoring its levels may help predict treatment outcomes or the development of drug resistance.

4. Predicting Treatment Response: One of the major challenges in epilepsy treatment is the identification of patients who will respond to specific therapies. miRNAs could potentially serve as biomarkers for predicting how a patient will respond to a particular drug or therapeutic intervention. This could lead to more individualized treatment plans, improving the chances of controlling seizures and minimizing side effects.

5. Monitoring Seizure Activity and Status Epilepticus: miRNAs such as miR-134 have been implicated in status epilepticus (SE), a medical emergency characterized by prolonged seizure activity. Monitoring circulating miRNAs during SE could help assess the severity of the condition and guide therapeutic interventions.

The study of circulating miRNAs as biomarkers of epilepsy represents a promising area of research in the quest for more accurate, non-invasive diagnostic tools and improved treatment strategies for epilepsy. The ability to measure specific miRNAs in easily accessible samples such as blood or serum holds great potential for enhancing our understanding of the molecular mechanisms underlying epilepsy, as well as providing real-time monitoring of disease progression and treatment outcomes. While there is substantial promise, further research is needed to validate specific miRNA biomarkers for clinical use, as well as to address the challenges related to their sensitivity, specificity, and standardization. As our understanding of miRNAs continues to grow, it is likely that they will play a central role in the future of epilepsy management, offering a new avenue for personalized medicine in this complex neurological disorder.

Epilepsy is a complex neurological disorder characterized by recurrent, unprovoked seizures that affect approximately 50 million people worldwide. It can be classified into different forms based on etiology, seizure type, and neurophysiological characteristics. Despite its prevalence, there is a significant gap in the early diagnosis and effective treatment of epilepsy. Traditionally, the diagnosis of epilepsy relies heavily on clinical evaluation, electroencephalography (EEG), and neuroimaging, but these methods are not always sufficient to determine the underlying molecular mechanisms of the disease or predict the response to therapy.

In recent years, the discovery of circulating microRNAs (miRNAs) has garnered attention as a potential source of non-invasive biomarkers for various diseases, including epilepsy. MicroRNAs are small non-coding RNA molecules that regulate gene expression post-transcriptionally by binding to the 3' untranslated regions (UTRs) of target mRNAs, leading to their degradation or translational repression. These miRNAs have been found to be involved in a variety of biological processes such as neuronal development, synaptic plasticity, and neuronal excitability, all of which are disrupted in epilepsy.

This article aims to review the emerging role of circulating miRNAs as biomarkers for different forms of epilepsy. We explore their potential to aid in the diagnosis, prognosis, and monitoring of treatment response, as well as the challenges and limitations of utilizing these biomarkers in clinical practice.

METHODS

To explore the current understanding of circulating miRNAs as biomarkers for epilepsy, we conducted a systematic review of recent studies published between 2015 and 2024. A thorough search was carried out using PubMed, Google Scholar, and Scopus, with keywords such as "circulating microRNAs," "epilepsy," "biomarkers," "seizures," and "diagnostic biomarkers." Only peer-reviewed articles in English, including original research studies, clinical trials, meta-analyses, and reviews, were included.

Studies were selected based on their relevance to the role of circulating miRNAs in epilepsy, including their association with specific epilepsy syndromes (e.g., temporal lobe epilepsy, genetic epilepsies, or drug-resistant epilepsy), their potential as diagnostic or prognostic tools, and their ability to monitor treatment outcomes. After selecting eligible studies, data were extracted, including information about the specific miRNAs identified, their expression profiles in different epilepsy forms, and the methodologies used to analyze miRNA levels in patient samples (such as blood, serum, plasma, or cerebrospinal fluid). Key findings were synthesized and analyzed to determine the clinical

relevance of circulating miRNAs in epilepsy.

RESULTS

1. MicroRNA Profiles in Epilepsy

Recent studies have identified several circulating miRNAs that are differentially expressed in patients with epilepsy, which may serve as potential biomarkers for different forms of the disorder. Notably, miRNAs are stable in peripheral blood, which makes them ideal candidates for non-invasive diagnostic tests.

- **Temporal Lobe Epilepsy (TLE)**

Temporal lobe epilepsy is the most common form of drug-resistant epilepsy. Studies have shown that miRNAs such as miR-146a, miR-155, and miR-29a are upregulated in the blood and serum of patients with TLE. These miRNAs are believed to play roles in neuroinflammation and neuroplasticity, which are key features of TLE pathology. miR-146a, for instance, has been shown to modulate inflammatory pathways and could serve as an indicator of epileptogenesis in TLE patients.

- **Genetic Epilepsies**

In genetic forms of epilepsy, such as Dravet syndrome and Lennox-Gastaut syndrome, altered miRNA expression has been observed. miR-34a and miR-124, both involved in neural differentiation and synaptic function, have been found to be downregulated in these patients. These miRNAs may serve as potential biomarkers for genetic epilepsy syndromes, as they are involved in the regulation of ion channels and neurotransmitter systems that are disrupted in these conditions.

- **Drug-Resistant Epilepsy**

Drug-resistant epilepsy (DRE) is a major clinical challenge, as a significant proportion of patients do not respond to conventional anticonvulsant medications. miRNAs such as miR-199a, miR-29b, and miR-132 have been implicated in DRE. For example, miR-199a has been associated with the regulation of drug resistance in epilepsy through its involvement in neuronal excitability and apoptosis. Elevated levels of miR-199a in serum have been proposed as a biomarker for predicting drug resistance and tailoring more individualized treatment approaches.

- **Status Epilepticus**

Status epilepticus (SE) is a life-threatening condition characterized by prolonged seizures. Circulating miRNAs such as miR-134 and miR-182 have been shown to be differentially expressed in patients with SE. These miRNAs may help in monitoring disease progression and assessing the severity of seizures. For example, miR-134, which regulates synaptic plasticity and dendritic growth, is believed to play a role in the exacerbation of SE, making it a potential biomarker for acute epileptic events.

2. Technological Advancements in miRNA Detection

The detection of miRNAs in blood samples is facilitated by technologies such as quantitative PCR (qPCR), next-generation sequencing (NGS), and microarray analysis. Recent advancements in these technologies have improved the sensitivity and specificity of miRNA detection, allowing for the identification of subtle differences in miRNA expression profiles between patients with different epilepsy forms.

The use of serum and plasma samples is particularly promising due to the ease of collection and the ability to monitor miRNA changes over time. Liquid biopsy techniques, which analyze miRNAs from cerebrospinal fluid (CSF) or plasma, are also being explored to monitor patients with epilepsy. These techniques allow for more precise tracking of disease progression and treatment response.

DISCUSSION

The identification of circulating miRNAs as biomarkers for epilepsy represents a significant step forward in the field of epilepsy diagnostics and personalized medicine. miRNAs are involved in many critical biological processes, including neuronal development, synaptic function, and neuroinflammation, all of which play essential roles in the pathophysiology of epilepsy. The ability to measure miRNA levels in easily accessible samples, such as blood or serum, holds great potential for non-invasive, real-time monitoring of epilepsy and its complications.

However, there are still several challenges to be addressed before miRNAs can be fully integrated into clinical practice. The variability in miRNA expression due to factors such as age, comorbidities, and medications must be carefully considered. Standardization of miRNA detection methods and large-scale clinical validation studies are essential to establish their clinical utility and to determine their sensitivity and specificity as diagnostic or prognostic biomarkers for epilepsy. Additionally, miRNAs can be influenced by other neurological conditions, making it necessary to distinguish epilepsy-specific miRNAs from those associated with other neurological disorders.

While the potential of circulating miRNAs as biomarkers is promising, more research is needed to identify specific miRNA profiles that can reliably differentiate between different forms of epilepsy. Longitudinal studies are also required to evaluate how miRNA levels change over time, particularly in response to treatment, to determine

their role in predicting treatment outcomes or relapse in drug-resistant epilepsy.

CONCLUSION

Circulating microRNAs have emerged as potential biomarkers for various forms of epilepsy, offering a non-invasive means of diagnosis, prognosis, and treatment monitoring. The differential expression of miRNAs in different epilepsy syndromes, such as temporal lobe epilepsy, genetic epilepsies, drug-resistant epilepsy, and status epilepticus, highlights their potential role in precision medicine. While technological advances in miRNA detection methods have enhanced the sensitivity and specificity of these biomarkers, further research and clinical validation are needed to establish their utility in routine clinical practice. The development of miRNA-based diagnostic tools could ultimately provide valuable insights into the molecular mechanisms of epilepsy and improve patient care through more personalized therapeutic strategies.

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