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EXPLORING THE ROLE OF miRNA's IN DRUG-RESISTANT EPILEPSY. A LITERATURE REVIEW

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Abstract

Background: Drug-resistant epilepsy is a complex clinical problem with a multifactorial basis, including both environmental and genetic factors, affecting one in three patients. Understanding the genetic factors underlying this resistance may improve prognosis and support the development of new targeted therapies. This systematic review examines the potential of microRNA (miRNA)-based therapies in overcoming pharmacoresistance, exploring their role in modulating epileptogenic processes and serving as biomarkers for personalized treatment.

Aim: The aim of this study is to explore the important role of miRNA expression in the development of drug-resistant epilepsy by conducting a systematic review using databases such as Scopus, PubMed, Google Scholar, Lilacs, and Cuiden.

Search strategy: A systematic review of the literature was conducted using the Scopus, PubMed, Google Scholar, and SciVerse databases. Data from news articles, press releases, or websites were excluded. The search covered the last 5 years (2019–2024) and was performed in PubMed, Scopus, and Web of Science databases. Relevant articles were cited, focusing on topics closely related to the subject of this study. The literature review specifically investigated the role of miRNA in drug-resistant epilepsy and included open-access review articles in the field of epilepsy. The article was prepared as part of a study funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant No. AP23489425).

Results: During the open-access literature search, 112 articles in English were identified. Duplicate publications, animal studies, and publications in languages other than English were excluded from the evaluation. After careful review, 32 articles were selected for full analysis.

Conclusion: Expanding research on the heritability of drug-resistant epilepsy through miRNA studies, particularly in Kazakhstan, will facilitate early diagnosis, improve treatment approaches, and ultimately enhance patient quality of life.

Keywords: *Drug-resistant epilepsy; microRNA; seizure; epileptogenesis; antiepileptic drugs.*

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Резюме

ИЗУЧЕНИЕ РОЛИ МИКРОРНК В ЛЕКАРСТВЕННО-УСТОЙЧИВОЙ ЭПИЛЕПСИИ. ОБЗОР ЛИТЕРАТУРЫ

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Введение: Лекарственно-устойчивая эпилепсия представляет собой сложную клиническую проблему многофакторного характера, включающего как влияние окружающей среды, так и генетические факторы, затрагивающую одного из трёх пациентов. Понимание генетических механизмов, лежащих в основе этой устойчивости, может улучшить прогноз заболевания и способствовать разработке новых таргетных терапевтических подходов. В данном систематическом обзоре рассматриваются перспективы применения терапий на основе микроРНК (miRNA) для преодоления фармакорезистентности, их роль в модуляции эпилептогенеза, а также потенциал в качестве биомаркеров для персонализированного лечения.

Цель: Целью данного исследования является изучение значимой роли экспрессии микроРНК в развитии лекарственно-устойчивой эпилепсии посредством проведения систематического обзора с использованием баз данных Scopus, PubMed, Google Scholar, Lilacs и Cuiden.

Стратегия поиска: Был проведен систематический обзор литературы с использованием баз данных Scopus, PubMed, Google Scholar и SciVerse. Источники, такие как новостные статьи, пресс-релизы и материалы с сайтов, были исключены из рассмотрения. Поиск охватывал публикации за последние 5 лет (2019–2024 годы) в базах данных PubMed, Scopus и Web of Science. Были проанализированы релевантные статьи, непосредственно связанные с тематикой исследования. В обзор включались в основном статьи открытого доступа, посвящённые роли микро РНК в лекарственно-устойчивой эпилепсии. Статья подготовлена в рамках исследования, финансируемого Комитетом науки Министерства науки и высшего образования Республики Казахстан (грант № AP23489425).

Результаты: В результате поиска литературы открытого доступа было выявлено 112 статей на английском языке. Из рассмотрения были исключены дублирующиеся публикации, исследования на животных и публикации на других языках. После тщательного отбора для полного анализа были выбраны 32 статьи.

Заключение: Расширение исследований наследственных факторов лекарственно-устойчивой эпилепсии с использованием анализа микроРНК, особенно в Казахстане, будет способствовать ранней диагностике, совершенствованию методов лечения и, в конечном итоге, улучшению качества жизни пациентов.

Ключевые слова: *лекарственно-устойчивая эпилепсия; микроРНК; приступ; эпилептогенез; противоэпилептические препараты.*

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Түйіндеме

ДӘРІГЕ ТӨЗІМДІ ЭПИЛЕПСИЯДА МИКРОРНҚ-ЛАРДЫҢ РӨЛІН ЗЕРТТЕУ. ӘДЕБИЕТТІК ШОЛУ

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Кіріспе: Дәріге төзімді эпилепсия – қоршаған орта және генетикалық факторларды қамтитын көпфакторлы күрделі клиникалық мәселе болып табылады және әрбір үшінші науқаста кездеседі. Бұл төзімділіктің генетикалық негіздерін түсіну аурудың болжамын жақсартып, жаңа мақсатты терапиялық тәсілдерді дамытуға мүмкіндік береді. Осы жүйелі шолуда фармакорезистенттілікті еңсеруде микроРНҚ (miRNA) негізіндегі терапиялардың әлеуеті, олардың эпилептогенез үдерістерін модуляциялаудағы рөлі және дербестендірілген ем үшін биомаркерлер ретінде қолданылу мүмкіндіктері қарастырылады.

Мақсаты: Осы зерттеудің мақсаты - Scopus, PubMed, Google Scholar, Lilacs және Cuiden дерекқорларын пайдалана отырып жүйелі шолу жүргізу арқылы дәріге төзімді эпилепсияның дамуына микроРНҚ экспрессиясының маңызды рөлін зерттеу.

Іздеу стратегиясы: Scopus, PubMed, Google Scholar және SciVerse дерекқорларында әдебиеттерге жүйелі шолу жүргізілді. Жаңалықтар мақалалары, баспасөз хабарламалары және веб-сайт материалдары шолудан шығарылды. Іздеу соңғы 5 жылды (2019–2024) қамтыды және PubMed, Scopus және Web of Science базаларында жүргізілді. Зерттеу тақырыбына тікелей қатысты мақалалар таңдалып алынды. Шолу негізінен эпилепсия саласындағы микроРНҚ рөліне арналған ашық қолжетімді мақалаларды қамтыды. Бұл мақала Қазақстан Республикасы Ғылым және жоғары білім министрлігінің Ғылым комитеті қаржыландыратын зерттеу жобасы аясында дайындалды (Грант № AP23489425).

Нәтижелер: Ашық қолжетімді әдебиеттерді іздеу нәтижесінде ағылшын тіліндегі 112 мақала анықталды. Қайталанатын жарияланымдар, жануарларға жүргізілген зерттеулер және ағылшын тілінен басқа тілдердегі мақалалар бағалауға енгізілмеді. Мұқият іріктеуден кейін толық талдау үшін 32 мақала таңдап алынды.

Қорытынды: Қазақстанда микроРНҚ зерттеулері арқылы дәріге төзімді эпилепсияның тұқым қуалаушылығын зерттеуді кеңейту ерте диагностиканы жеңілдетеді, емдеу тәсілдерін жақсартады және нәтижесінде пациенттердің өмір сүру сапасын арттырады.

Түйінді сөздер: *дәріге төзімді эпилепсия; микроРНҚ; ұстама; эпилептогенез; эпилепсияға қарсы препараттар.*

Дәйексөз үшін: *Досжанов И.А., Нурдинов Н.С., Абилов Т.С., Садыкова К.Ж., Нускабаева Г.О., Жаркынбекова Н.А., Ошибаева А.Е., Аймаханов М.С.* Дәріге төзімді эпилепсияда микроРНҚ-лардың рөлін зерттеу. Әдебиеттік шолу // ғылым және Денсаулық сақтау. 2025. Vol.27 (1), Б.167-173. *doi 10.34689/SH.2024.27.1.020*

Introduction

Epilepsy is a common and severe neurological disorder characterized by recurrent seizures, affecting 0.5% to 1% of the population in developed countries and even more in developing regions [1], [2]. According to the latest International League Against Epilepsy (ILAE) classification, seizures are categorized as focal, generalized, or of unknown onset. Types of epilepsy include generalized, focal, and a newly combined category, which helps in selecting appropriate antiepileptic drugs (AEDs) [4]. Regardless of the cause, recurrent seizures lead to various physical, psychological, and social challenges, which can largely be mitigated through effective seizure control.

The primary goal of antiepileptic treatment is to achieve seizure freedom. While many patients gain good control with AED therapy, approximately one-third experience seizures resistant to these treatments, a condition known as drug-resistant epilepsy (DRE). DRE is associated with increased morbidity and mortality, along with psychosocial and cognitive difficulties, ultimately reducing quality of life [5]. The factors contributing to drug resistance are complex, involving a combination of environmental, genetic, disease-related, and drug-related influences. Research suggests that microRNAs (miRNAs) play a crucial role in drug resistance mechanisms by modulating gene expression and influencing neuronal pathways [6], [7], [8].

The definition of drug resistance has evolved over time, typically focusing on the number of treatment failures, the endpoint (e.g., seizure freedom), and the time required to achieve this endpoint. According to statistics, approximately 7% to 20% of children and 30% to 40% of adults exhibit resistance to pharmacological intervention.

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small, non-coding RNA molecules, typically 21–25 nucleotides in length, that play a key role in regulating gene expression [9]. They exert their effects by binding to complementary sequences in target messenger RNAs (mRNAs), leading to either mRNA degradation or inhibition of its translation. This post-transcriptional regulation allows miRNAs to finely tune gene expression across a wide range of biological processes.

The biogenesis of miRNAs is a multistep process that includes transcription, processing, export, maturation, and functional regulation. Initially, miRNAs are transcribed from DNA by RNA polymerase II or III, forming primary miRNA (pri-miRNA) transcripts. Pri-miRNA is then processed in the nucleus by the Drosha enzyme within a microprocessor complex to form precursor miRNA (pre-miRNA). This short, hairpin-like precursor is exported to the cytoplasm via Exportin-5, where it undergoes further processing by the Dicer enzyme, generating a double-stranded RNA molecule. One strand of this duplex is incorporated into the RNA-induced silencing complex (RISC), while the other strand is typically degraded (Figure 1) [10].

The miRNA within the RISC complex then targets mRNAs, leading to their degradation or translational repression, ultimately regulating gene expression. This finely tuned process allows miRNAs to play pivotal roles in various biological functions and cellular processes [10].

The Role of MicroRNAs in Epileptogenesis

Epileptogenesis, the process by which epilepsy develops following an initial insult such as a stroke or traumatic brain injury, occurs in three distinct phases: acute, latent, and chronic. The latent phase is characterized by molecular and structural changes in the brain, including neuronal loss, inflammation, and synaptic reorganization, which eventually lead to recurrent spontaneous seizures. However, the precise mechanisms underlying these processes remain unclear. As epilepsy progresses into the chronic phase, the condition worsens over time, highlighting the urgent need for novel treatment strategies [11].

Recent studies have underscored the pivotal role of microRNAs (miRNAs) in the regulation of epileptogenesis, offering promising therapeutic avenues, particularly in drug-resistant epilepsy (DRE). miRNAs are crucial in neuronal

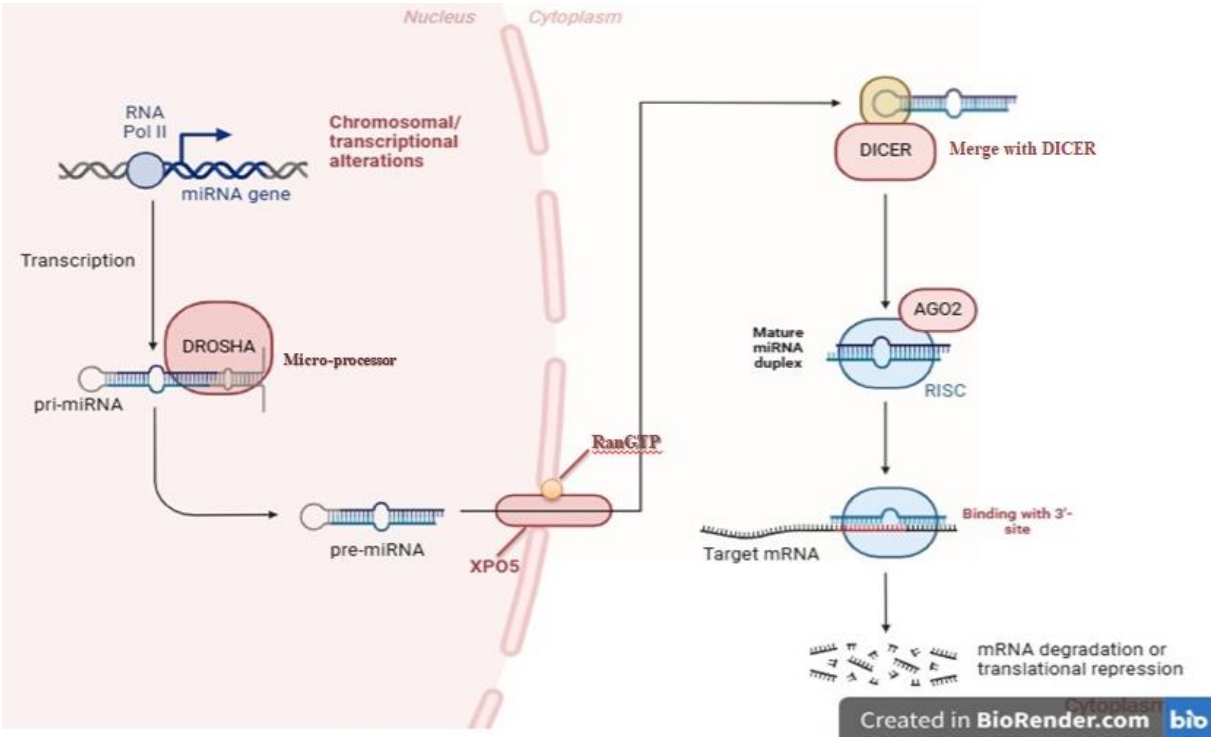

Figure 1. Biogenesis of miRNAs (created by the author using BioRender.com).

development, synaptic plasticity, and neuroprotection, influencing differentiation, learning processes, and responses to injury. They also play a key role in modulating inflammation, neuronal excitability, and synaptic transmission, making their dysregulation a potential contributor to epilepsy pathophysiology [12].

Among the identified miRNAs, miR-324-5p has been recognized as a key regulator of neuronal excitability. Experimental models have demonstrated that altering its expression can significantly influence seizure susceptibility, suggesting its potential as a therapeutic target for seizure control in DRE. Similarly, miR-335-5p has been shown to regulate voltage-gated sodium channel (VGSC) expression, with its increased levels reducing seizure severity and improving survival rates, whereas its inhibition enhances susceptibility to seizures [13].

Moreover, integrative network analyses of miRNA and mRNA expression profiles during epileptogenesis have provided deeper insights into the dynamic regulatory mechanisms involved. These studies have identified differentially expressed miRNAs throughout epilepsy progression, further reinforcing their potential as biomarkers and therapeutic targets. The evaluation of circulating miRNAs as preclinical biomarkers has also shown promise in predicting the risk of epileptogenesis. Their minimally invasive nature offers an opportunity for early diagnosis and intervention, potentially improving clinical outcomes for individuals at risk of developing epilepsy.

Furthermore, therapeutic strategies aimed at modulating miRNA expression are actively being investigated to combat DRE. Approaches such as miRNA mimics and inhibitors are being explored to restore the balance of dysregulated miRNAs, potentially enhancing the efficacy of existing antiepileptic drugs (AEDs) [12]. These innovative strategies not only hold the potential to improve patient outcomes but also pave the way for personalized treatment regimens based on an individual's unique miRNA profile.

Collectively, these findings emphasize the critical involvement of miRNAs in epileptogenesis and drug resistance, highlighting their potential role in the development of novel therapeutic strategies and diagnostic tools. Further research into miRNA-based interventions may provide a significant breakthrough in epilepsy management, particularly for patients with drug-resistant forms of the disorder.

Additionally, miRNAs serve as powerful modulators of post-transcriptional gene expression and are significantly dysregulated throughout epileptogenesis (Figure 1). Their dynamic expression patterns make them valuable molecular biomarkers for diagnosing epilepsy, assessing the risk of its development, and monitoring treatment response. As ongoing research continues to identify and validate key miRNAs involved in epilepsy pathophysiology, their clinical application as diagnostic and prognostic tools is becoming increasingly feasible (Table 1).

The first study on miRNAs in human epilepsy, published in 2010, identified increased hippocampal levels of miR-146a, which is associated with the regulation of inflammatory responses [14]. Subsequent research focused on five specific miRNAs: miR-132, miR-34a, miR-134, miR-184, and miR-128, each demonstrating potential importance in different physiological and pathological contexts [14], [15], [16], [17]. Notably, in mouse models, inhibition of miR-134 after status epilepticus significantly reduced the onset of spontaneous seizures [18], while reduced expression of miR-128 led to increased motor activity and fatal epilepsy [17].

Recent targeted and genome-wide miRNA profiling studies have identified more than 100 miRNA alterations in epilepsy patients and animal models, suggesting that epilepsy is associated with widespread changes in miRNA expression [19].

Table 1.

Key miRNA biomarkers in the diagnosis, prediction, and management of epileptogenesis.

№	MicroRNAs	Disease	Function	References
1	miR-146a	Epilepsy as a neurodegenerative disease	Control of apoptosis	Srinivasan et al., 2013
2	miR-211-5p	Epilepsy, ferroptosis	Regulates neuronal ferroptosis and oxidative stress associated with epilepsy.	X. Li et al., 2024
3	miR-335-5p	Epilepsy, adeno-associated virus	Suppresses the expression of voltage-gated sodium channels and may be a target for seizure control.	Heiland et al., 2023
4	mirR-34c-5p	Epilepsy, hippocampal neuron damage	In drug-resistant epilepsy, miR-34c-5p downregulation enhances neuroinflammation, exacerbating hippocampal neuronal loss.	Fu et al., 2020
5	miR-485	Hippocampal epilepsy	Overexpression significantly reduces seizure frequency and epileptiform firing of hippocampal DG neurons.	K. Wang et al., 2021
6	miR-146a, miR-134	Epilepsy	Improve blood flow in patients with drug-resistant seizures.	Leontariti et al., 2020, Organista-Juárez et al., 2019
7	miR-146a, miR-155, miR-134, miR-21, miR-22	Drug-resistant epilepsy	Predicted any reductions in seizures with the modified Atkins diet in adult patients with DRE after three months	Samões et al., 2024
8	miR-146a	Drug-resistant epilepsy	Reduced expression is associated with predisposition to drug-resistant epilepsy.	Boschiero et al., 2020
9	miR-146a	Drug-resistant epilepsy	Functional polymorphism of the miR-146a gene is associated with drug-resistant epilepsy and seizure frequency.	Cui et al., 2015
10	miR-139-5p	Epilepsy	Confers antiepileptic drug sensitivity in refractory epilepsy via inhibition of MRP1.	L. Wang et al., 2020
11	miR-212-3p and miR-132-3p	Mesial temporal lobe epilepsy (MTLE)	Both miRNAs work synergistically to control Sox11 expression	Haenisch et al., 2015

miRNA Profile in Brain Tissues of Patients with Drug-Resistant Epilepsy

In recent decades, with the development of next-generation sequencing (NGS), biomarker studies aimed at identifying diagnostic and prognostic miRNAs have become more widespread. The gold standard research design for these studies includes a discovery phase and validation phases, during which candidate biomarkers are selected from large sets of molecules. In the discovery phase, high-throughput technologies such as microarrays and RNA sequencing are used for sample profiling. Due to their high costs, both arrays and RNA sequencing allow for the identification of hundreds of compounds, though often in limited patient populations. This can lead to small sample sizes and higher rates of false positives and negatives, requiring additional testing. During the validation phase, quantitative PCR (qPCR) remains the gold standard for sensitivity and reliability, although it is also costly [20].

Traditional miRNA profiling studies in pharmacoresistant epilepsy are limited because tissue biopsies can only be obtained from patients undergoing brain surgery after the failure of other therapies. The lack of comparison with non-seizure, drug-sensitive patients and the limited number of samples hinder the understanding of large-scale miRNA dysregulation and the creation of independent discovery and validation cohorts. Additionally, samples are typically collected after therapeutic failure, making it difficult to assess the effect of an antiepileptic drug (AED) on miRNA levels [21], [22], [23].

This field still requires significant high-throughput profiling using NGS to identify miRNAs specific to drug-resistant epilepsy (DRE) patients. *Zucchini et al.* (2014) conducted the first rare tissue miRNA profiling study on 14 paraffin-embedded hippocampal or temporal lobe samples from DRE patients with hippocampal sclerosis. Although the study primarily focused on granule cell pathology (GCP), it also investigated the role of miRNAs in pharmacoresistance. The researchers identified miR-487a as the most significantly dysregulated miRNA in DRE patients [24].

De Matteis et al. found that miR-301a-3p was significantly overexpressed in a patient with drug-resistant mesial temporal lobe epilepsy (mTLE) who died of sudden unexpected death in epilepsy. Among the miRNAs studied miR-301a-3p, miR-194-5p, miR-30b-5p, miR-342-5p, and miR-4446-3p only miR-301a-3p showed significant dysregulation in both the tissue and plasma of patients with epilepsy compared to a non-epileptic control group [25].

Bencurova et al. also detected miR-301a-3p using NGS but did not observe a similar pattern in a larger qPCR cohort. They examined post-mortem changes and found a decrease in miRNA levels after 32 hours, suggesting strong stability. Their study, the first to use high-throughput NGS in DRE tissue, identified novel differentially expressed miRNAs (miR-1260a, miR-1260b, and miR-4443) associated with disorders other than epilepsy [26].

In contrast, well-studied miRNAs such as miR-146a, miR-132-3p, miR-132-5p, and miR-134-5p did not show changes in expression due to the unique profile of the hippocampus. *Organista-Juarez et al.* found a positive correlation between miR-146a levels, the number of AEDs used, and seizure frequency, suggesting a compensatory function in neuroinflammation [2].

Che et al. conducted an exploratory biomarker study in DRE patients with localized cortical dysplasia and found strong validity for miR-323a-5p [27]. Similarly, *Sun et al.* (2016) observed an increase in miR-129-2-3p in the same cohort. Another study found that miR-4521 was differentially regulated. These studies included various approaches, such as ROC analysis, AUC values, and confidence intervals, though sensitivity or specificity data were not published [28], [29].

Lee et al. [30] and *Gong et al.* [31] found that miR-153 plays a role in refractory epilepsy by affecting the HIF-1α pathway. In the discovery phase, Lee et al. found that miR-153 expression was downregulated in DRE patients, while HIF-1α expression was upregulated in non-epileptic controls. Both studies indicated that miR-153 targets the 3' UTR region of HIF-1α. Overexpression of miR-153 inhibits HIF-1α, while inhibition of miR-153 increases HIF-1α levels, suggesting a regulatory function of miR-153 in pharmacoresistance [30], [31].

Zorin et al. (2018) mentioned that different physiological parameters should be used to predict the course of epilepsy. Using cluster analysis and logistic regression, the research team identified patterns that could help predict drug resistance. These methods can also be applied to study genetic markers, providing new insights into the mechanisms of drug resistance [32].

Conclusion. Based on the analysis of the scientific literature, it is evident that expanding research on the heritability of drug-resistant epilepsy through miRNA studies is crucial, particularly in relation to risk factors prevalent in the region of Kazakhstan. The presented information enhances applied knowledge for primary care physicians and hospitals, contributing to improved early diagnosis and prevention of epileptic disorders in the future.

Integrating genetic and physiological data can significantly enhance the prediction of drug-resistant epilepsy. A review of the literature on the role of miRNA in drug-resistant epilepsy underscores the need for further research in this area. Such studies have the potential to facilitate the development of new antiepileptic drugs, improve the accuracy of timely diagnosis, refine treatment strategies, and support socio-psychological interventions. These advancements will positively influence the prescription of appropriate medications, the optimization of drug dosages, and, ultimately, the social functioning and quality of life for patients with epilepsy.

Conflict of interest. *The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.*

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