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Trends and Hotspots of microRNAs in Epilepsy: A 10-Year Cross-Sectional Study

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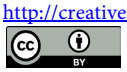

Abstract

miRNAs regulate a variety of target proteins and signaling pathways associated with epilepsy. We conducted a cross-sectional study of publications associated with microRNA in epilepsy in the past 10 years using bibliometric methods. Our results showed that the number of publications elevated gradually, peaking in 2020. Countries/institutions collaboration network showed that extensive international cooperation between countries existed and China published the most of papers in this field. USA, Ireland, and other Western countries are also active in this field. Moreover, we identify the most influential authors and publications. Last, Keyword co-occurrence network indicated miR-146a, miR-155 and miR-132 were hotspots and the most studied microRNAs, miR-146a, miR-155 and miR-132 may be potential targets and more mechanisms associated with microRNA in epilepsy will be found.

Subject Areas

Allergy & Clinical Immunology

Keywords

Epilepsy, microRNAs, Cross-Sectional Study, Bibliometrics

1. Introduction

Epilepsy represents a common chronic neurological disorder with a high disability rate, affecting more than 50 million people worldwide [1]. However, the pathogenesis of epilepsy has not yet been fully elucidated. And the treatment of epilepsy still faces many difficulties. The current anti-epileptic drugs are more of a blockage of the disease process and do not directly target the cause of seizures. So most of the seizures are still recurrent and cannot be cured at the root after being controlled by drugs.

MicroRNA (miRNA) is a non-coding ribonucleic acid, about 19 - 22 nt in length, which plays an important role in the post-transcriptional regulation of gene expression [2] [3]. It has been found that some miRNAs are involved in the regulation of epileptogenesis and maintenance, which exert neuroprotective effects through various mechanisms involving apoptosis, synaptic regulation, etc [4]. For example, MiR-34a inhibits neuronal apoptosis in epilepsy by inhibiting activated caspase-3 protein [4]. MiRNA-344a may have a minor regulatory effect on epilepsy-induced cortical apoptotic signaling pathways, but the specific target is unknown. MiR-134 inhibitor exerts neuroprotective effects by upregulating hippocampal limk1 expression and downregulating cofilin expression in SE rats [5].

Bibliometrics are increasingly being used for research evaluation methodology, which offers a quantitative approach to analyzing academic literature in a specific field [6] [7]. But there is no bibliometric study of microRNAs in epilepsy. So we aim to examine trends and hotspots of microRNAs in epilepsy through the past 10-year publications to guide the research directions.

2. Methods

All publications were from Web of Science Core Collection of the Web of Science (WOS). Retrieval Strategy was TS = ("microRNA" and "epilepsy"). The timespan ran between 2001-01-01 and 2021-12-31. Only articles and reviews were included. Meeting Abstracts, Editorial Materials, Letters, Book Chapters, Corrections, Retractions, Data Papers, Proceedings Papers and Retracted Publications were excluded. Then HistCite, VOS viewer and excel were used for bibliometric analysis (**Figure 1**).

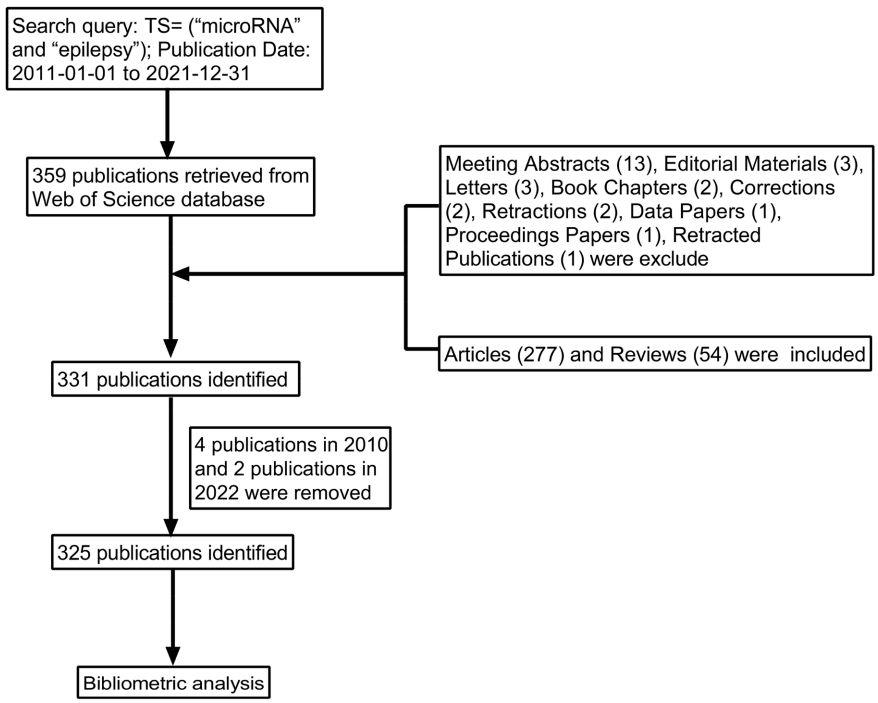

Figure 1. The flow chart of data collection.

3. Results

3.1. Annual Scientific Production

Up to 325 publications including reviews (54) and articles (277) in the field of microRNAs in epilepsy were retrieved. A total of 1814 authors published these papers. Overall, publications related to microRNAs in epilepsy are increasing. As shown in Figure 2, the publication volume peaked in 2020 (52).

3.2. Countries, Institutions and Authors

Up to 41 countries were identified. China published the most papers and achieve the highest local cited scores (LCS) (Table 1). USA and other European countries such as Ireland, Germany and Netherlands were also active in this field. Figure 3 shows a network visualization map of national collaborations. In addition, up to 515 institutions were identified. Royal Coll Surgeons Ireland published the highest number of articles (Table 2). Figure 4 shows a network visualization map of institutions. Royal Coll Surgeons Ireland published the highest number of publications in the field and achieved the highest local cited scores (Table 3). In addition, Henshall DC became the most productive and high-cited researcher.

Table 1. Top 10 countries with the highest number of publications.

Rank	Country	Number of Publications	LCS
1	China	166	559
2	USA	57	208
3	Ireland	38	225
4	Germany	26	113
5	Netherlands	22	179
6	UK	16	98
7	Italy	15	54
8	Brazil	13	6
9	Finland	10	23
10	Denmark	8	68

Table 2. Top 10 institutions with the largest number of publications.

Rank	Institution	Number of Publications	LCS
1	Royal Coll Surgeons Ireland	36	207
2	Univ Amsterdam	15	87
3	Cent S Univ	13	161
4	Capital Med Univ	12	40
5	Beaumont Hosp	10	53
6	Harbin Med Univ	10	25
7	Cent South Univ	9	21
8	Fudan Univ	9	2
9	Univ Eastern Finland	9	19
10	Univ Med Ctr Utrecht	9	86

Table 3. Top 10 authors with the highest number of publications.

Rank	Authors	Number of Publications	LCS
1	Henshall DC	37	225
2	Jimenez-Mateos EM	16	66
3	Aronica E	14	87
4	Brennan GP	14	72
5	Rosenow F	13	67
6	Engel T	12	30
7	Reschke CR	12	48
8	Bauer S	11	52
9	van Vliet EA	10	68
10	Delanty N	9	53

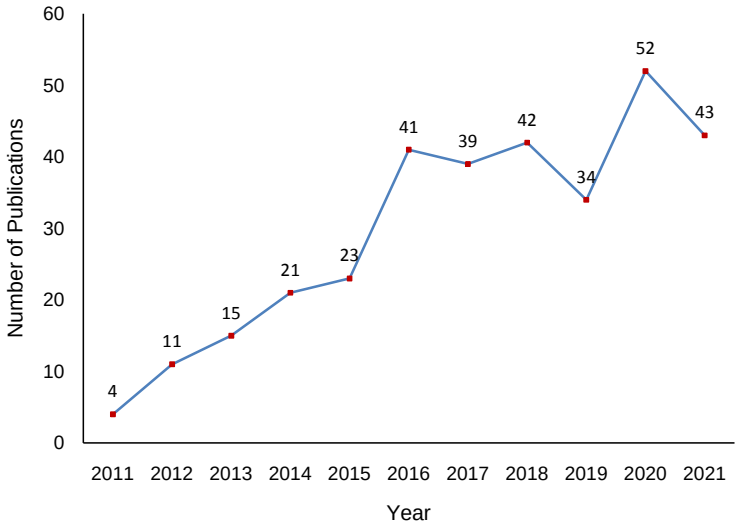

Figure 2. Yearly output.

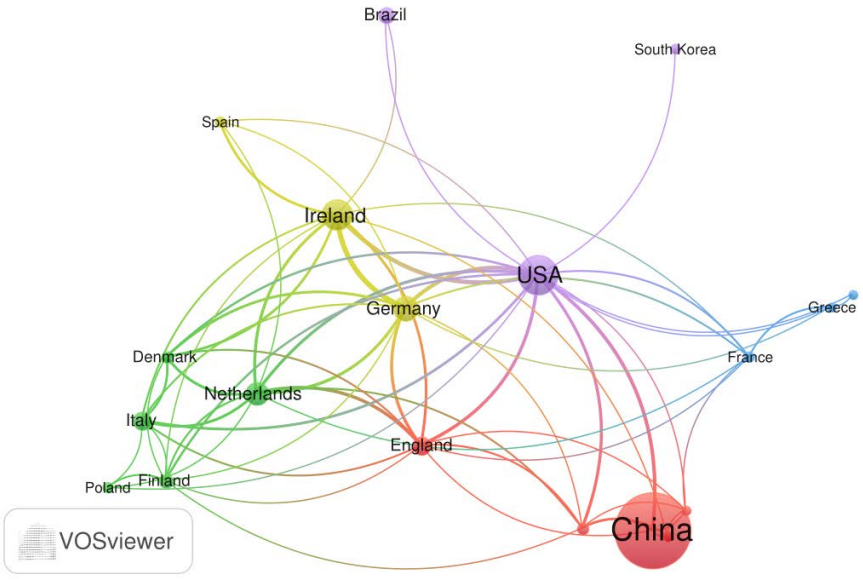

Figure 3. Network diagram of cooperation between countries.

Figure 4. Network diagram of cooperation between institutions.

3.3. Articles and Journals

The top 10 highly-cited articles were shown in **Table 4**. The article published in 2012, written by Kan, AA, entitled "Genome-wide microRNA profiling of human temporal lobe epilepsy identifies modulators of the immune response", achieved the highest number of citations. Moreover, a total of 176 Journals participated in 325 publications in this field. SCIENTIFIC REPORTS published the most papers but EPILEPSIA achieved the highest local cited scores (**Table 5**, **Table 6**).

3.4. Keywords

As is shown in **Figure 5**, a great number of keywords and links between these words informed co-occurrence network. For example, miR-146a, miR-155 and miR-132 were the most studied microRNA, circled with red box in **Figure 5**. In addition, "Epilepsy", "microRNA", "Inflammation", "Apoptosis" and "NF-Kappa-B" were also included, which indicates microRNA may regulate inflammation, apoptosis and NF-Kappa-B signal to influence epilepsy.

4. Discussion

The 10-year cross-sectional study found that the number of annual publications climbs gradually, peaking in 2020. Moreover, Most of research in this field has been done by China, USA, Ireland, and other Western countries. Extensive international cooperation between countries existed. Last, miR-146a, miR-155 and miR-132 were the most studied microRNA.

miR-146a is increased in hippocampus in rat model of epilepsy and patients with epilepsy (PWD) [4] [8] [9] [10]. In addition, miR-146a was found up-regulated in serum of PWD and may be a biomarker for epilepsy. Evidence from clinical studies also suggests that the rs57095329 polymorphism in the promoter region of miR-146a is associated with genetic susceptibility and seizure frequency of drug-resistant epilepsy [11] [12] [13]. Inflammatory response plays a crucial role in epilepsy [14] [15]. miR-146a can exert a pro-inflammatory effect via forming a miR-146a-CFH-IL-1 beta loop circuit and then leads to cause exacerbation of epilepsy [16]. In refractory epilepsy, suppressing the miR-146a gene can reduce pathogenic alterations while also improving medication resistance via regulating HMGB1/TLR4/NF-kB signaling pathway [17]. In addition, silencing miRNA-146a can reduce neuronal injury via down-regulating Notch-1 in the lithium chloride-pilocarpine rat models [18].

Table 4. Top 10 Highly-cited articles.

Rank	Title	Author	Journal	Year	LCS
1	Genome-wide microRNA profiling of human temporal lobe epilepsy identifies modulators of the immune response	Kan, AA	CELL MOL LIFE SCI	2012	63
2	Temporal lobe epilepsy induces differential expression of hippocampal miRNAs including let-7e and miR-23a/b	Song, YJ	BRAIN RES	2011	63
3	Hippocampal subregion-specific microRNA expression during epileptogenesis in experimental temporal lobe epilepsy	Gorter, JA	NEUROBIOL DIS	2014	61
4	Expression profile of microRNAs in rat hippocampus following lithium-pilocarpine-induced status epilepticus	Hu, K	NEUROSCI LETT	2011	54
5	Interleukin-1 beta and microRNA-146a in an immature rat model and children with mesial temporal lobe epilepsy	Omran, A	EPILEPSIA	2012	50
6	MicroRNA and epilepsy: profiling, functions and potential clinical applications	Henshall, DC	CURR OPIN NEUROL	2014	47
7	Expressions of Tumor Necrosis Factor Alpha and MicroRNA-155 in Immature Rat Model of Status Epilepticus and Children with Mesial Temporal Lobe Epilepsy	Ashhab, MU	J MOL NEUROSCI	2013	37
8	Expression profiling the microRNA response to epileptic preconditioning identifies miR-184 as a modulator of seizure-induced neuronal death	McKiernan, RC	EXP NEUROL	2012	35
9	MicroRNA-128 Governs Neuronal Excitability and Motor Behavior in Mice	Tan, CL	SCIENCE	2013	32
10	Different MicroRNA Profiles in Chronic Epilepsy Versus Acute Seizure Mouse Models	Kretschmann, A	J MOL NEUROSCI	2015	24

Table 5. Top 10 Highly-productive articles.

Rank	Journal	Number of Publications	LCS
1	SCIENTIFIC REPORTS	13	0
2	PLOS ONE	12	0
3	EPILEPSY RESEARCH	11	52
4	FRONTIERS IN MOLECULAR NEUROSCIENCE	11	0
5	EPILEPSIA	9	134
6	BRAIN RESEARCH	8	126
7	NEUROBIOLOGY OF DISEASE	8	84
8	MOLECULAR MEDICINE REPORTS	7	15
9	NEUROCHEMICAL RESEARCH	7	15
10	JOURNAL OF MOLECULAR NEUROSCIENCE	6	73

Table 6. Top 10 Highly-cited articles.

Rank	Journal	LCS	Number of Publications
1	EPILEPSIA	134	9
2	BRAIN RESEARCH	126	8
3	NEUROBIOLOGY OF DISEASE	84	8
4	JOURNAL OF MOLECULAR NEUROSCIENCE	73	6
5	NEUROSCIENCE LETTERS	66	3
6	CELLULAR AND MOLECULAR LIFE SCIENCES	63	1
7	EPILEPSY RESEARCH	52	11
8	CURRENT OPINION IN NEUROLOGY	47	1
9	EXPERIMENTAL NEUROLOGY	37	2
10	CELL REPORTS	36	2

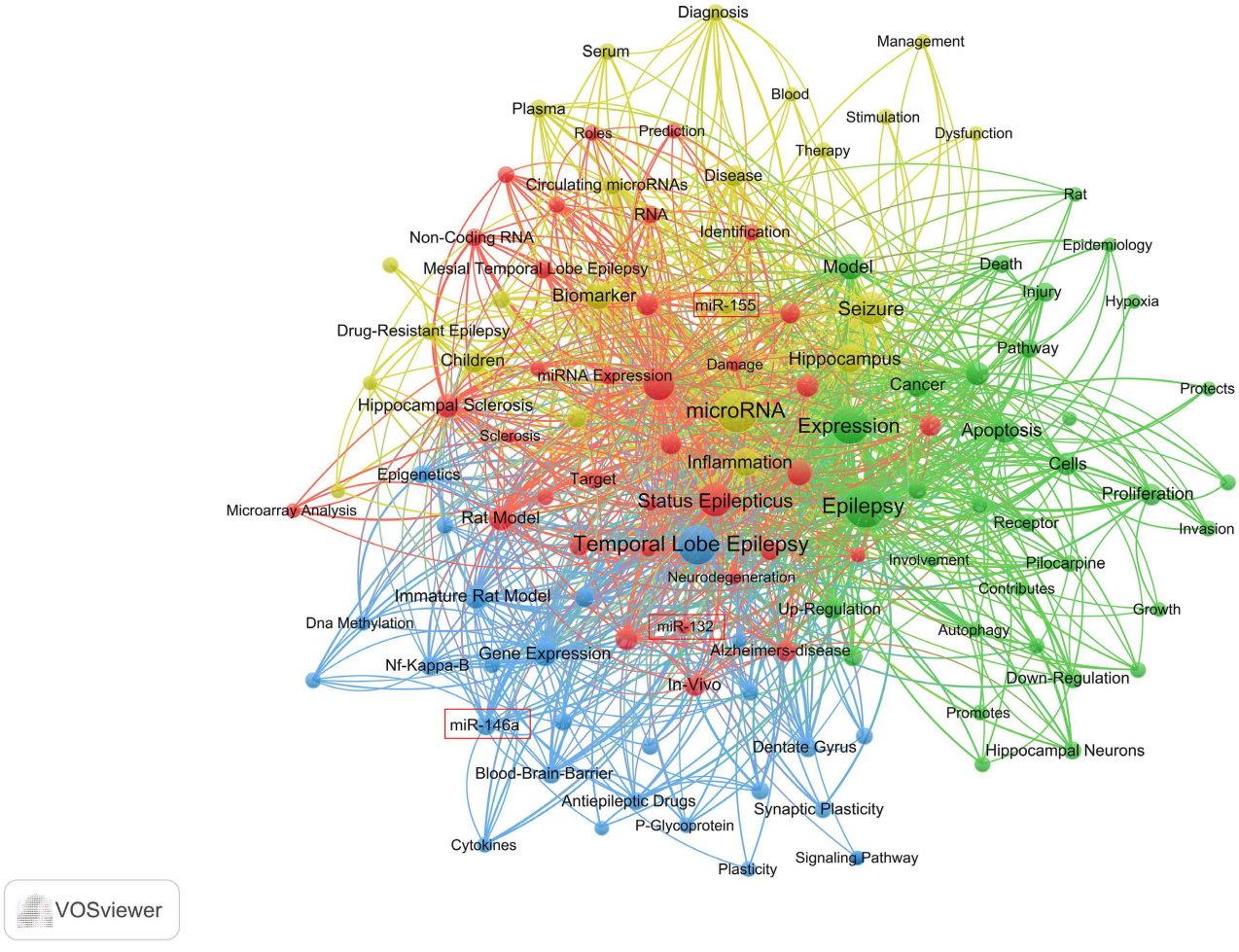

Figure 5. Keywords co-occurrence network.

miR-155 exerts a crucial role in controlling inflammatory responses and apoptosis signaling associated with epilepsy [19]-[26]. miR-155 expression is

elevated in model of epilepsy and PWD [19] [22] [23] [25] [27]. On the one hand, miR-155 may regulate neuroinflammatory responses by interacting with TNF-α [22]. On another hand, this miRNA can also induce neuronal apoptosis via regulating Sestrin-3, BDNF and PI3K/Akt/mTOR signaling pathway [23] [24] [25].

In the dynamic control of neuronal development, maturation, and functioning, miR-132 plays a role in axon growth, neural migration, and plasticity [28]. MiR-132 was upregulated in the Three Stages (The latent stage, acute and chronic stages) of MTLE (Mesial Temporal Lobe Epilepsy) and in Immature Rats Children with MTLE [29]. In vitro and in vivo studies showed that miR-132 could promote epileptogenesis and progression of epilepsy by modulating dendritic spines, reducing neuronal apoptosis, and altering neuronal excitability [30] [31] [32]. Moreover, Bioinformatics suggests that miR-132 not only promotes primary epilepsy, but it also promotes glioma-induced epilepsy [33].

5. Conclusion

microRNAs in epilepsy remain an active field, with a large number of microRNAs shown to be associated with epilepsy. Especially, miR-146a, miR-155 and miR-132 can cause exacerbation of epilepsy and are hot spots for research in epilepsy. miR-155 regulates inflammatory responses and apoptosis signaling associated with epilepsy. miR-146a can induce inflammation, neuronal injury and medication resistance. Modulating dendritic spines, reducing neuronal apoptosis, and altering neuronal excitability may be responsible for miR-132 exacerbating epilepsy. More and more microRNAs associated with epilepsy will be found and mechanisms related to epilepsy will be eluted in the future.

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Conflicts of Interest

The authors declare no conflicts of interest.

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