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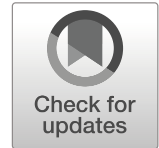

A Systematic Review of MicroRNA Expression as Biomarker of Late-Onset Alzheimer's Disease

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Abstract

Late-onset Alzheimer's disease (LOAD) is a high-occurrence neurological disorder but the difficulty in identifying precise and early biomarkers has complicated the understanding of the disease and the development of new treatments. In this sense, important knowledge is emerging regarding novel molecular and biological candidates with diagnostic potential, including microRNAs (miRNAs), which have a key role in gene repression. The aim of this systematic review was to define the role of miRNAs' expression as biomarkers for LOAD both in brain tissues, which could help understand the biology of the disease, and circulating tissues, which could serve as non-invasive markers of the pathology. A systematic search was performed in Web of Science and PubMed using the keywords ((Alzheimer or Alzheimer's) and (microRNA or microRNAs or miRNA or miRNAs or miR)) until August 2018 to retrieve all articles that presented independent original data evaluating the impact of miRNA expression on the development of LOAD in human population. A total of 90 studies investigating the role of miRNAs' expression in the development of LOAD were identified. While other widely studied miRNAs such as hsa-miR-146a presented contradictory results among studies, deregulation in brain tissue of seven miRNAs, hsa-miR-16-5p, hsa-miR-34a-5p, hsa-miR-107, hsa-miR-125-5p, hsa-miR-132-3p, hsa-miR-181-3p, and hsa-miR-212-3p, was consistently identified in LOAD patients. Their role in the disease could be mediated through the regulation of key pathways, such as axon guidance, longevity, insulin, and MAPK signaling pathway. However, regarding their role as non-invasive biomarkers of LOAD in fluids, although the limited results available are promising, further studies are required.

Keywords Late-onset Alzheimer's disease · Circulating · Non-circulating · MicroRNAs · Expression

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a prevalence of almost 50 million people around the world. In fact, it is the most common cause of dementia worldwide [1, 2]. AD can be classified in two categories depending on onset age: early-onset Alzheimer's disease (EOAD), the development of which starts before the patients are 65 years old, and late-onset Alzheimer's disease (LOAD), which begins at a higher age [3, 4].

These disorders have a heterogeneous origin. While several markers have been established as risk factors for EOAD [4, 5], identifying precise and early biomarkers for LOAD has proven to be more difficult, which complicates the understanding of the disease and the development of new treatments [6].

In this sense, important knowledge is emerging regarding novel molecular and biological candidates with diagnostic potential, including microRNAs (miRNAs). miRNAs conform a subclass of small non-coding RNAs that play a significant regulatory role appointing mRNAs for cleavage or translational repression [7]. Actually, more than 60% of human genes are regulated by miRNAs, which are present in most body tissues, including brain tissue, cerebrospinal fluid (CSF), or serum [8,

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9]. As a result, deregulation of miRNAs is crucial in the pathogenesis of neurodegenerative diseases [10]. Therefore, the expression of miRNAs collected from brain tissue biopsies could serve as a new biomarker and help understand the biology of LOAD [10]. Furthermore, recent findings indicate that miRNAs present in biofluids such as blood or CSF, known as circulating miRNAs [11], could reflect the composition of the brain extracellular space fluid and serve as non-invasive biomarkers of the disease [12].

Here, we have conducted a systematic review aiming to define a specific profile of deregulated miRNAs, both non-circulating and circulating, associated with the development of LOAD in order to identify precise biomarkers for the disease, as well as possible explanations for their involvement in the disorder. This may contribute to clarify the current state of this topic and establish the basis for future research.

Material and Methods

Systematic Review

Search Strategy

In order to retrieve all the published evidence related to miRNA expression and their association with LOAD, a systematic search was performed in Web of Science, using Web of Science Core Collection [13], and in PubMed database [14] using the Best Match algorithm. The keywords employed in the current search strategy were: Alzheimer or Alzheimer's and microRNA or microRNAs or miRNA or miRNAs or miR. The search covered articles published until August 2018.

Inclusion and Exclusion Criteria

Articles were included if they presented independent original data and evaluated the impact of miRNA expression on the development of LOAD in human population. Hence, reviews or meta-analyses, case reports, abstracts, letters or comments, methodological studies, and articles not published in English were excluded. Studies were also excluded if they did not analyze miRNAs, did not include data from human populations or control groups, and were focused on other diseases or had different aims. After full-text evaluation, articles were also excluded if they did not specify miRNA expression, did not provide the mean age of participants, did not focus on LOAD, or did not compare miRNA expression in LOAD patients with a control group.

Data Extraction

Eligibility for inclusion of each evaluated study was independently assessed by two reviewers (SH and BS) and disagreements were resolved by consensus. After study selection, reviewers extracted the following information from each study: publication year, type of sample analyzed, characteristics of the study population, methodology used, number of miRNAs assessed, list of significant miRNAs provided, and their regulation status (upregulated, downregulated, or unchanged) in LOAD patients vs. controls. The significance level was set at p value < 0.05, according to the statistical method established in each article. In order to analyze the data, a unification of tissue sources was carried out in non-circulating studies. The following areas were classified as the frontal cortex lobe: Brodmann area 6, Brodmann area 9, Brodmann area 10, frontal cortex, frontal gyrus, medial frontal gyrus, and gray and white matter; the following areas were classified as the temporal cortex lobe: Brodmann area 20, Brodmann area 22, temporal cortex, temporal lobe cortex, temporal gyrus, and temporal lobe neocortex; the following areas were classified as the parietal cortex lobe: parietal lobe and parietal cortex; the CA 1 region was classified as the hippocampus.

On a first step, miRNAs that presented the same regulation status in four or more articles were selected. In order to minimize publication bias, selected miRNAs were searched in the supplementary material of the rest of the included articles to determine whether they had been analyzed in those articles with non-significant results. Then, miRNAs to be considered for further analyses were selected based on the following criteria:(a) that they did not present contradictory results, that is, they did not present an upregulated status and a downregulated status in different studies performed with the same kind of sample source; and b) that the ratio for that specific miRNA were 2:1 or higher taking into account the number of studies finding statistically significant differences in expressions comparing LOAD patients and controls, and those that did not find any differences.

Data Analysis

Selection of Target Genes

To predict the putative target genes of the selected miRNAs, miRWalk 2.0 database [15] was used. Only those genes predicted by 7 or more of the 12 miRNA-target prediction algorithms available at miRWalk were considered.

Pathway Enrichment Analysis

Pathway enrichment analyses were performed with the over-representation analysis module of the ConsensusPathDB web tool (CPdB) [16]. KEGG [17], Reactome [18], and BioCarta [19] pathway databases were used to analyze the lists of predicted target genes and determine the overrepresented pathways, assuming a conservative p value cutoff of 0.0001.

Venn Diagram

In order to study and establish concordances in the regulation status of miRNAs in Alzheimer's patients regarding analyses in brain tissues and fluids, InteractiVenn tool [20] and Bioinformatics & Evolutionary Genomics [21] were used.

Results

Search Results

A total of 1727 records were discovered following the search parameters, 884 in PubMed and 843 in Web of Science (Main Collection). After removing duplicated articles, 1007 remained. Of these, 878 were excluded after abstract review because they did not met the inclusion criteria. Full texts of the 129 remaining studies focused on miRNAs in human LOAD were evaluated thoroughly. As a result, 39 additional studies were excluded at this step because they did not compare miRNA expressions between LOAD patients and healthy controls. Finally, 90 studies investigating the role of miRNAs expression in the development of LOAD were included. These articles were classified according to the source of sample analyzed (brain tissue or fluids): 42 of them provided data on non-circulating miRNAs (brain tissue), whereas 54 studied circulating miRNAs (fluids) (Fig. 1). Results regarding non-circulating and circulating miRNAs are presented separately in the following sections.

Non-circulating miRNAs

Forty-two studies analyzed non-circulating miRNA to search for differences in expression between LOAD cases and healthy controls (Online Resource Supplementary Table 1) [22–63]. As a result, a total of 319 different miRNAs were found to be deregulated in LOAD patients in at least one study.

Then, we identified 11 miRNAs that presented the same regulation status in at least 4 studies (Table 1) although some of them presented contradictions in additional studies. Seven miRNAs were mainly donwregulated: hsa-miR-9-5p [25, 27, 32, 42, 49, 51, 54, 59–61, 63], hsa-miR-16-5p [27, 30, 40, 42, 60], hsa-miR-29-3p [36, 40, 54, 58, 60, 64], hsa-miR-107 [27, 30, 42, 62], hsa-miR-132-3p [23, 27, 31, 35, 38, 39, 44–46, 59–61, 63] and hsa-miR-181a/c/d-5p [26, 27, 39, 54, 58, 60], and hsa-miR-212-3p [23, 27, 31, 39, 46, 60]; while, four miRNAs were mostly upregulated: hsa-miR-34a-5p [25, 42, 48, 51, 52], hsa-miR-125a/b-5p [25, 27, 40, 48, 49, 51, 59, 60, 63], hsa-miR-146a-5p [25, 27, 34, 42, 48, 49, 51, 56, 59–61], and hsa-miR-155-5p [25, 27, 34, 48, 49, 51, 53, 60]. The only miRNA that did not show any contradiction was hsa-miR-212-3p, which was downregulated in the 6 studies in which it was analyzed [23, 27, 31, 39, 46, 60].

Since the studies were performed analyzing miRNAs in different cerebral areas, mainly temporal, frontal or parietal lobe cortex, among other, we looked for correlations between specific brain regions and precise regulation status. However, due to the limited number of studies within each category, it was not possible to identify a clear correlation and, as a result, all results were evaluated together.

Therefore, we focused on the miRNAs that did not present contradictions (upregulated and downregulated in different studies) and that had a high ratio (2:1 or more) of significant vs. non-significant results. As a result, 7 miRNAs were selected for further analyses: hsa-miR-16-5p, hsa-miR-107, hsa-miR-132-3p, hsa-miR-181a/c/d-5p, and hsa-miR-212-3p met the established criteria for downregulation, while hsa-miR-34a-5p and hsa-miR-125a/b-5p were mainly upregulated (Table 2).

Predicted target genes for hsa-miR-16-5p, hsa-miR-34a-5p, hsa-miR-107, hsa-miR-125a/b-5p, hsa-miR-132-3p, hsa-miR-181a/c/d-5p, and hsa-miR-212-3p were searched in order to identify significantly overrepresented pathways regulated by those miRNAs and linked with LOAD. The 9 pathways that were most significantly overrepresented are shown in Online Resource Supplementary Table 2.

Among the most significant pathways, axon guidance (Online Resource Supplementary Fig. 1), longevity regulating pathway (Online Resource Supplementary Fig. 2), insulin signaling pathway (Online Resource Supplementary Fig. 3), and MAPK (Online Resource Supplementary Fig. 4) signaling pathway were the ones that were associated with a highest number of the selected miRNAs and had a plausible mechanistical connection with LOAD (Table 3 and Online Resource Supplementary Table 2).

Axon guidance was overrepresented among the predicted target genes of hsa-miR-34a-5p, hsa-miR-125a/b-5p, and hsa-miR-132-3p, which represented 41.1% of the genes in the pathway. Longevity regulating pathway was associated with hsa-miR-132-3p and hsa-miR-212-3p, with coverage of 22.6% of the pathway. Insulin signaling pathway, which is associated with the longevity process, was associated with hsa-miR-16-5p and hsa-miR-107, their predicted target genes covering a 35% of the pathway. Finally, MAPK signaling pathway was overrepresented among hsa-miR-16-5p and hsa-miR-125a/b-5p target genes (30.5% coverage).

Circulating miRNAs

Fifty-four studies compared the expression of circulating miRNAs in LOAD cases vs. healthy controls using different tissue sources (CSF, serum, plasma, blood, monocytes, and lymphocytes) [27, 28, 33, 42, 49, 51, 60, 64–111].

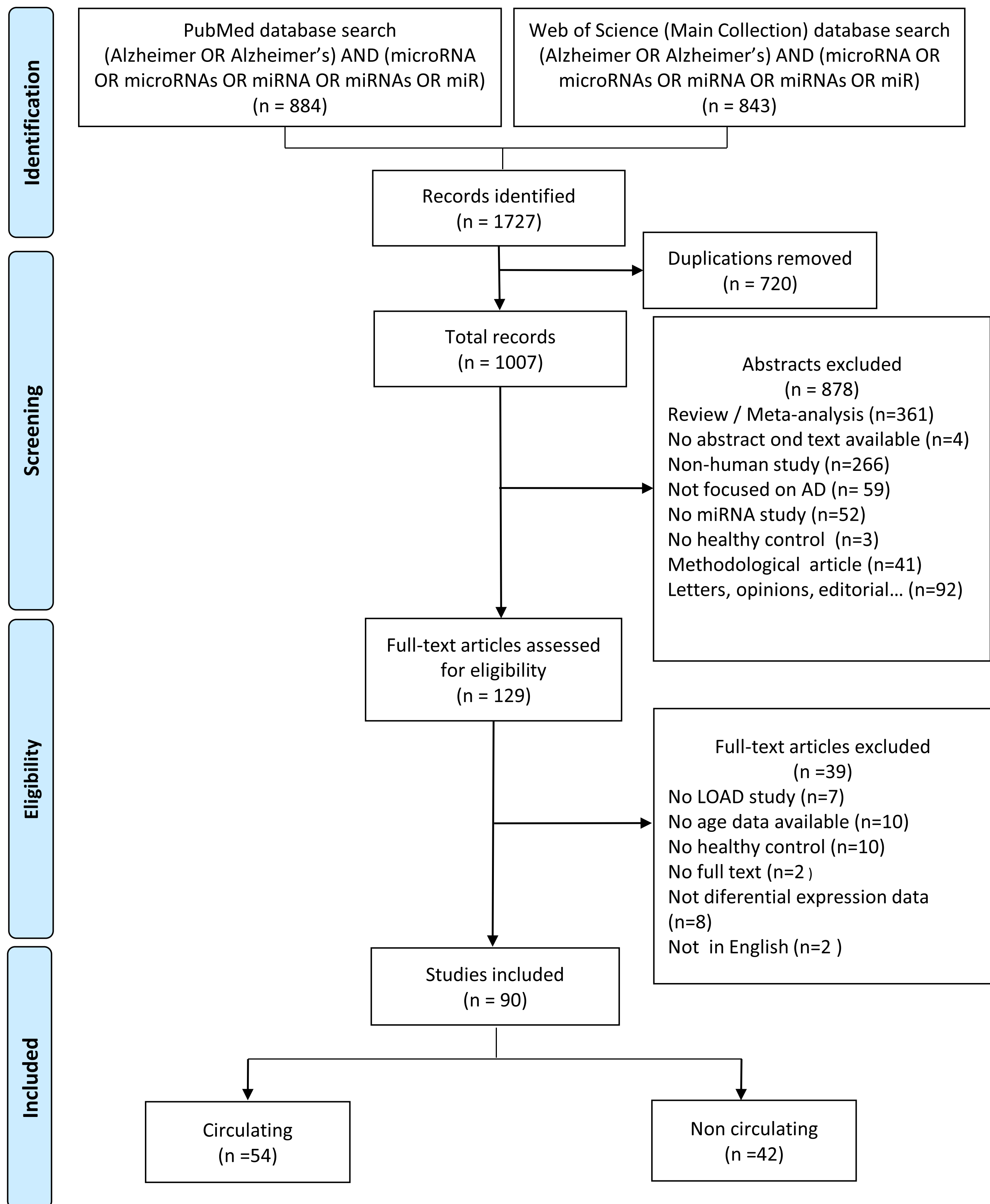

Fig. 1 Flowchart of study selection through the systematic search. A total of 54 circulating studies and 42 non-circulating articles were included

Characteristics of those studies are shown in Online Resource Supplementary Table 3.

These 54 studies identified a total of 271 different miRNAs that presented significant changes in expressions between

Table 1 Non-circulating miRNAs concluded to be deregulated in 4 or more studies

Significant miRNAs	Regulation	AD (*N*)	Ctrl (*N*)	miRNA analyzed	Sample source	Reference	Method
hsa-miR-9-5p	Up	6	6	6	Temporal cortex	Alexandrov et al. 2012	Array
		6	6	856 / 243		Sethi and Lukiw 2009	Array
		5	5	12		Lukiw et al. 2012	RT q-PCR
		5	5	13	Hippocampus	Lukiw et al. 2007	Array
		9	6	3	Brain	Jesko et al. 2016	Array
	Down	10	7	242	Cerebellum Hippocampus Frontal cortex	Cogswell et al. 2008	RT q-PCR
		7	7	–	Neocortex	Geekiyanage and Chan 2011	RT q-PCR
		27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
	NS	23	23	3	Neocortex	Lukiw et al. 2008	Array
		10	11	9	Hippocampus	Muller et al. 2014	RT q-PCR
		26	19	2650	Temporal cortex	Pogue and Lukiw 2018	Array
hsa-miR-16-5p	Down	10	11	9	Hippocampus	Muller et al. 2014	RT q-PCR
		10	7	242	Cerebellum	Cogswell et al. 2008	RT-qPCR
		27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
		12	12	6	Hippocampus	Moncini et al. 2017	RT q-PCR
	NS	12	12	6	Cerebellum	Moncini et al. 2017	RT q-PCR
		10	5	8	Frontal cortex	Banzhaf-Strathmann et al. 2015	RT q-PCR
hsa-miR-29a-3p	Up	10	7	242	Frontal cortex	Cogswell et al. 2008	RT-qPCR
	Down	7	7	–	Neocortex	Geekiyanage and Chan 2011	RT q-PCR
hsa-miR-29b-3p	Up	10	7	242	Frontal cortex	Cogswell et al. 2008	RT q-PCR
	Down	7	7	–	Neocortex	Geekiyanage et al. 2012	RT q-PCR
		10	5	8	Frontal cortex	Banzhaf-Strathmann et al. 2014	RT q-PCR
		10	5	8		Banzhaf-Strathmann et al. 2015	RT q-PCR
		4	4	470	Parietal cortex	Nunez-Iglesias et al. 2010	Array
hsa-miR-29c-3p	Down	31	29	1	Frontal cortex	Lei et al. 2015	RT q-PCR
		4	4	470	Parietal cortex	Nunez-Iglesias et al. 2010	Array
hsa-miR-34a-5p	Up	5	5	12	Temporal cortex	Lukiw et al., 2012	RT q-PCR
		26	19	2650		Pogue and Lukiw 2018	Array
		29	20	1	Hippocampus	Agostini et al. 2011	RT q-PCR
		3	3	1898		Zhao et al. 2013	Array
	NS	10	11	9		Muller et al. 2014	RT q-PCR
hsa-miR-107	Down	27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
		6	6	200 / 70		Wang et al. 2008	RT q-PCR
		12	12	6		Moncini et al. 2017	RT q-PCR
		10	11	9	Hippocampus	Muller et al. 2014	RT q-PCR
		12	12	6		Moncini et al. 2017	RT q-PCR
	NS	12	12	6	Cerebellum	Moncini et al. 2017	RT q-PCR
hsa-miR-125a-5p	Up	27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
hsa-miR-125b-5p	Up	6	6	6		Alexandrov et al. 2012	Array
		27	18	474		Hara et al. 2017	miRNAseq
		5	5	12		Lukiw et al. 2012	RT q-PCR
		26	19	2650		Pogue and Lukiw 2018	Array
		6	6	856 / 243		Sethi and Lukiw 2009	Array
		10	7	242	Cerebellum	Cogswell et al. 2008	RT q-PCR
		10	7	242	Hippocampus	Cogswell et al. 2008	RT q-PCR
		3	3	1898		Zhao et al. 2013	Array

Table 1 (continued)

Significant miRNAs	Regulation	AD (*N*)	Ctrl (*N*)	miRNA analyzed	Sample source	Reference	Method
		10	7	242	Frontal cortex	Cogswell et al. 2008	RT q-PCR
		10	5	8		Banzhaf-Strathmann et al. 2015	RT q-PCR
		9	10	1	Brain	Ma et al. 2017	RT q-PCR
	NS	5	5	13	Hippocampus	Lukiw et al. 2007	Array
hsa-miR-132-3p	Down	5/9 5	5/9 5	-	Hippocampus Temporal cortex	Annese et al. 2018	miRNAseq
		5	5		Frontal cortex		
		10	7	242	Hippocampus Frontal cortex Cerebellum	Cogswell et al. 2008	RT q-PCR
		27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
		5/8	2/8	795/2 (Val)		Hebert et al. 2013	Deep seq/RT q-PCR
		41/5 21/6	23/5 28/6	641/10 (Val) 641/10 (Val)	Hippocampus Frontal cortex	Lau et al. 2013	Deep seq/RT q-PCR
		8 39/8 39/225 39/8	8 25/8 25/87 25/8	10 1221/2 (Val)	Temporal cortex Frontal cortex	Pichler et al. 2017	Array/sqPCR
		39/8	25/8				
		7	5	1	Temporal cortex Hippocampus	Smith et al. 2015	RT q-PCR
		11	11		Temporal cortex		
		3/10	3/12	20 (Val)	Frontal cortex	Weinberg et al. 2015	Array/q-PCR
		6/16	6/16	40/2 (Val)	Temporal cortex	Wong et al. 2013	RT q-PCR
	NS	6	6	856/243		Sethi and Lukiw 2009	Array
		5	5	13	Hippocampus	Lukiw et al. 2007	Array
		23	23	3	Neocortex Hippocampus	Lukiw et al. 2008	Array
		7	7	1	Nucleus basalis of Meynert	Zhu et al. 2016	Hybridization
hsa-miR-146a-5p	Up	6	6	6	Temporal cortex	Alexandrov et al. 2012	Array
		36	30	2		Cui et al. 2010	Array
		5	5	12		Lukiw et al. 2012	RT q-PCR
		26	19	2650		Pogue and Lukiw 2018	Array
		6	6	856/243		Sethi and Lukiw 2009	Array
		12	6	2650		Zhao et al. 2016	Array
		23	23	3	Neocortex	Lukiw et al. 2008	Array
		3	3	1898	Hippocampus	Zhao et al. 2013	Array
	Down	10	7	242	Frontal cortex	Cogswell et al. 2008	RT q-PCR
		27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
		10	11	9	Hippocampus	Muller et al. 2014	RT q-PCR
hsa-miR-146b-5p	Down	10	7	242	Cerebellum Hippocampus Frontal cortex	Cogswell et al. 2008	RT q-PCR
		27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
hsa-miR-155-5p	Up	6	6	6	Temporal cortex	Alexandrov et al. 2012	Array
		12	6	2650		Zhao et al. 2016	Array
		5	5	12		Lukiw et al. 2012	RT q-PCR
		3	3	1898	Hippocampus	Zhao et al. 2013	Array

Table 1 (continued)

Significant miRNAs	Regulation	AD (*N*)	Ctrl (*N*)	miRNA analyzed	Sample source	Reference	Method
	Down	10	7	242	Cerebellum	Cogswell et al. 2008	RT q-PCR
		27	18	474	Temporal cortex	Hara et al. 2017	miRNA-seq
	NS	26	19	2650		Pogue and LukIw 2018	Array
		12	6	7	Frontal cortex	Culpan et al. 2011	RT q-PCR
hsa-miR-181a-5p	Down	10	7	242	Cerebellum	Cogswell et al. 2008	RT q-PCR
	Down	3 / 10	3 /12	20 (Val)	Frontal cortex	Weinberg et al. 2015	Array/RT q-PCR
	NS	14	14	1	Hippocampus	Zumkehr et al. 2018	RT q-PCR
hsa-miR-181c-5p	Down	7	7	–	Neocortex	Geekiyanage and Chan 2011	RT q-PCR
	Down	4	4	470	Parietal lobe	Nunez-Iglesias et al. 2010	Array
hsa-miR-181d-5p	Down	27	18	474	Temporal cortex	Hara et al. 2017	miRNAseq
hsa-miR-212-3p	Down	5 / 9	5 / 9		Hippocampus	Annese et al. 2018	miRNAseq
		10	7	242		Cogswell et al. 2008	RT q-PCR
		5	5	-	Temporal cortex	Annese et al. 2018	miRNAseq
		3/10	3/12	20 (Val)		Weinberg et al. 2015	Array/sqPCR
		6/16	6/16	40/2 (Val)		Wong et al. 2013	RT q-PCR
		39/8	25/8	1221/2 (Val)		Pichler et al. 2017	Array/sqPCR
		27	18	474		Hara et al. 2017	miRNAseq
		5	5	-	Frontal cortex	Annese et al. 2018	miRNAseq
		39/225	25/87	1221/2 (Val)		Pichler et al. 2017	Array/sqPCR
		39/8	25/8	1221/2 (Val)		Pichler et al. 2017	Array/sqPCR
		39/8	25/8	1221/2 (Val)		Pichler et al. 2017	Array/sqPCR
		3/10	3/12	20 (Val)		Weinberg et al. 2015	Array/sqPCR
		10	7	242		Cogswell et al. 2008	RT q-PCR
		10	7	242	Cerebellum	Cogswell et al. 2008	RT q-PCR

Test, tested cohort; *Val*, validation cohort; *Up*, statistically significantly upregulated in LOAD patients; *NS*, no significant difference between patients and controls; *Down*, significantly downregulated in LOAD patients; *Seq*, sequencing; *sq.*, semiquantitative; *q*, quantitative

hsa-miR-181a/c/d-5p was considered the same miRNA. The same is true for hsa-mir-29a/b/c-3p, hsa-miR-125a/b-5p, and hsa-mir-146a/b-5p

patients and controls. However, none of the miRNAs was found to present the same deregulation status in four or more studies (Online Resource Supplementary Table 3).

When the seven miRNAs selected as the most promising non-circulating biomarkers (hsa-miR-16-5p, hsa-miR-34-5p, hsa-miR-107, hsa-miR-125a/b-5p, hsa-miR-132-3p, hsa-miR-181a/c/d-5p, and hsa-miR-212-3p) were studied in fluids, the obtained results were heterogeneous among miRNAs. On the one hand, hsa-miR-212-3p, which was the miRNA showing the most consistent results in brain tissue, has not been studied in any circulating tissues, and hsa-miR-16-5p, which was mainly downregulated in LOAD brain tissues, was found as unchanged in CSF in the 3 studies in which it was analyzed [42, 69, 75]. Additionally, while hsa-miR-34a-5p was mainly upregulated in brain tissue, the results are contradictory among studies regarding circulating tissues, both in CSF and blood-derived samples [72, 100].

On the other hand, while hsa-miR-181a/c/d-5p was found equally downregulated or unchanged in blood-derived samples from LOAD patients, it was mainly found downregulated in CSF, in accordance with the results found in brain tissue [60, 64, 99]. Likewise, hsa-miR-132-3p expression in CSF followed the same downregulation observed in brain tissue in the only study in which it was analyzed [99], while results in plasma and serum were contradictory [65, 112]. A similar tendency could be observed for hsa-miR-125-5p, blood-derived samples showing contradictory results, while it was mainly upregulated in CSF, especially when only hsa-miR-125a-5p was considered, which showed no contradiction among studies [60, 65]. By contrast, hsa-miR-107 followed the opposite tendency, with the two studies performed in CSF showing non-significant differences between LOAD and healthy individuals and the studies performed in blood-derived tissues mirroring the downregulation observed in brain tissues [86, 95, 108].

Finally, we performed an analysis to study the correlation between the miRNAs reported in brain tissue and fluids. miRNAs identified as differentially expressed in both

Table 2 Seven selected non-circulating deregulated miRNAs specifying their regulation status and brain area analyzed

miRNA	Downregulation	Upregulation	Non-significant
hsa-miR-16-5p	TLC: [27, 30] H: [30, 42] C: [60]		FLC: [40] C: [30]
hsa-miR-34a-5p	-	TLC: [25, 51] H: [48, 52]	H: [42]
hsa-miR-107	TLC: [27, 30, 62] H: [30, 42]		C: [30]
hsa-miR-125a-5p	-	TLC: [27]	
hsa-miR-125b-5p		TLC: [25, 27, 49, 59] B: [29] FLC: [40, 60] C: [40, 60] H: [48, 60]	H: [63]
hsa-miR-132-3p	TLC: [23, 27, 31, 38, 39, 44–46, 59] FLC: [23, 31, 38, 39, 45, 60] C: [60]	-	N: [61] TLC: [59] H: [61, 63] NBM: [35]
hsa-miR-181a-5p	FLC: [39] C: [60]	-	H: [26]
hsa-miR-181c-5p	N: [54] PLC: [58]	-	-
hsa-miR-181d-5p	TLC: [27]	-	-
hsa-miR-212-3p	TLC: [23, 27, 39, 46] FLC: [23, 31, 39, 60] C: [60] H: [23]	-	-

Downregulation, significantly downregulated in LOAD patients; upregulation, statistically significantly upregulated in LOAD patients; non-significant, no significant difference between patients and controls. *B*, brain; *C*, cerebellum; *FLC*, frontal lobe cortex; *N*, neocortex; *NBM*, nucleus basalis of Meynert; *H*, hippocampus; *PLC*, parietal lobe cortex; *TLC*, temporal lobe cortex

hsa-miR-181a/c/d-5p was considered as the same miRNA. The same is true for hsa-miR-125a/b-5p

circulating and non-circulating tissues were compared taking into account their regulation status (Online Resource Supplementary Fig. 5a and 5b), 20 and 61 commonly upregulated and downregulated miRNAs were identified, respectively (Online Resource Supplementary Tables 4 and 5). On the one hand, among the commonly upregulated miRNAs, in addition to those mentioned above, we could highlight hsa-miR-455-3p, upregulated in the three studies in which it was analyzed [24, 28, 107]. On the other hand, regarding the downregulated miRNAs, hsa-miR-191-5p and hsa-miR-495-3p presented concordant results in the four [27, 103, 107] and three [27, 45, 99] studies in which they were analyzed, respectively.

Discussion

The main aim of this systematic review was to define the role of miRNAs' expression as biomarkers for LOAD, both in brain tissues, which could help understand the biology of the disease, and circulating tissues, which could serve as non-invasive markers of the pathology.

It must be noted that we have specifically focused on those studies performed with LOAD patients, due to the difficulty in identifying biomarkers associated with this category of AD patients. Our extensive search strategy has allowed us to identify a total of 90 articles that met the inclusion criteria, 42 of them providing data on non-circulating miRNAs and 54 studies performed on circulating tissues, which represents a larger number of studies than the most recent systematic reviews in AD [113, 114].

Non-circulating miRNAs

We have identified 11 miRNAs that presented the same regulation status in at least 4 studies. However, four of them presented contradictory results among studies: hsa-miR-9-5p, hsa-miR-29-3p, hsa-miR-155-5p, and hsa-miR-146a-5p, the latter having been widely studied for its implication in

Table 3 Significantly overrepresented pathways among the predicted target genes of the 7 miRNAs selected in non-circulating tissues

Pathway Number of genes (database)	miRNA	*p* value	FDR	Number of gene targets	Pathway coverage
Axon guidance (*Homo sapiens*) (KEGG) 175 genes	hsa-miR-34a/c-5p	2.97E−06	1.32E−03	34 (19.4%)	74 (41.1%)
	hsa-miR-125a/b-3p	1.79E−05	3.44E−03	30 (17.1%)	
	hsa-miR-132-3p	2.58E−05	7.49E−03	24 (13.7%)	
Longevity regulating pathway-multiple species-Homo sapiens (human) (KEGG) 62 genes	hsa-miR-132-3p	2.25E−05	7.49E−03	13 (21.0%)	14 (22.58%)
	hsa-miR-212-3p	7.60E−05	0.0269	12 (19.4%)	
Insulin signaling pathway (KEGG) 137 genes	hsa-miR-16-5p	4.81E−10	1.00E−07	37 (27.0%)	48 (35.0%)
	hsa-miR-107	3.87E−07	1.36E−04	29 (21.2%)	
MAPK signaling pathway-Homo sapiens (human) (KEGG) 295 genes	hsa-miR-16-5p	9.98E−11	3.11E−08	62 (21.0%)	90 (30.5%)
	hsa-miR-125a/b-3p	2.28E−05	0.00383	43 (14.6%)	

neurodegeneration. Further studies would be needed in order to further explore the role of these miRNAs in LOAD and the reasons for the differences observed. In this review, we focused on the 7 miRNAs that were significantly deregulated in LOAD brain tissue in a mostly consistent way among studies.

First, hsa-miR-16-5p was analyzed in five different studies, being found downregulated in at least one brain region in LOAD patients in four of them [27, 30, 42, 60]. The only study that did not find any difference between patients and controls was the only one to be performed with samples from frontal cortex, which raised the question whether this difference in sample source was responsible for the difference in result. In fact, in one of the studies, mir-16-5p expression was measured in three different brain regions, being downregulated in LOAD temporal cortex and hippocampus but not in cerebellum, when compared with the same regions in healthy individuals [30]. Although, in the context of this review, it was difficult to establish associations between miRNA expression and brain regions, these results may indicate that miRNA expression related to LOAD may vary among certain specific brain regions and, thus, choosing the most appropriate sample source may be of great relevance.

Accordingly, miRNAs of the miR-181 family were downregulated in five out of the six studies in which they were analyzed [26, 27, 39, 54, 58, 60]. Once again, the only study that presented a contradicting result was performed considering a different brain region, the hippocampus, which might be to blame for the difference in result.

hsa-miR-107 was downregulated in LOAD patients in at least one of the brain regions analyzed in the four studies in which it was analyzed [27, 30, 42, 62]. Interestingly, it must be noted again that in one study it was analyzed in three different brain regions (temporal cortex, hippocampus, and cerebellum), being only unchanged in the cerebellum [30]. Therefore, this contributes to the idea that establishing an appropriate and standardized brain region for sample collection would be relevant for miRNA expression studies.

hsa-miR-132-3p was downregulated in nine out of thirteen articles in which it was analyzed [23, 27, 31, 35, 38, 39, 44–46, 59–61, 63], and hsa-miR-212-3p was downregulated in the six studies in which it was analyzed [23, 27, 31, 39, 46, 60]. In agreement with these results, the absence of these miRNAs has been shown to lead to programmed cell death [46], which would be a plausible mechanism for their involvement in LOAD.

By contrast, hsa-miR-34a-5p was upregulated in four out of five studies [25, 48, 51, 52]. It must be taken into account that in the study in which no difference in hsa-miR-34a-5p expression was observed between patients and controls, the control population [42] showed some initial neurodegeneration evidence (an average of I and II Braak stages), which could have contributed to an underestimation of differences in miRNA expression. Furthermore, hsa-miR-34a-5p has been previously reported to regulate neuronal differentiation and neurite outgrowth, and it has been shown to inhibit the expression of human tau by binding to its long 3′ UTR isoform [115], which supports a possible role in LOAD.

Finally, hsa-miR-125-5p was also upregulated in ten out of eleven studies [25, 27, 29, 40, 48, 49, 59, 60, 63]. In agreement with this result, upregulation of hsa-miR-125b-5p has been previously proposed to contribute to the degeneration of brain tissues [116] and it has been reported to play an important role in the mammalian neuronal development and differentiation [117, 118], which would explain its potential role in LOAD.

In order to further explore the role of these miRNAs in LOAD pathology, we performed an *in silico* analysis to identify the pathways regulated by these miRNAs that could be more related to the disease. To do so, we must take into consideration that, histopathologically, AD brains are characterized by two main hallmarks. On the one hand, amyloid β peptides (AβPs) are accumulated extracellularly generating plaques [119]. On the other hand, an intracellular accumulation of hyperphosphorylated tau protein leads to the formation of neurofibrillary tangles (NFTs) [120]. In addition, other modifications which are common to other neurodegenerative

diseases could contribute to cognitive impairment, such as neuron and synapses loss or neuroinflammation [121, 122].

Our results indicate that the main target pathways for the seven miRNAs selected in the brain tissue with a putative role in LOAD are axon guidance, longevity, insulin, and MAPK signaling pathway.

First, axon guidance pathway is involved in axon outgrowth, repulsion, or attraction. This pathway could be directly implicated in LOAD development due to the relevance of those processes in the formation of neuritic plaques (NPs). NPs are a specific subtype of amyloid β plaques, of relevance in LOAD, formed by extracellular accumulation of well-known AβPs and degenerating axons and dendrites [123]. This pathway is overrepresented among the putative targets of hsa-miR-34a-5p, hsa-miR-125a/b-5p, and hsa-miR-132-3p. Therefore, changes in the regulation of genes in those pathways as a result of the deregulation of those miRNAs could be of relevance in the context of LOAD. For instance, glycogen synthase kinase (*GSK3B*) is a specific predicted target gene of hsa-miR-132-3p, which is downregulated in LOAD patients. *GSK3B* has been previously associated with LOAD, considering its ability to promote tau hyperphosphorylation [124, 125]. Tau is a microtubule-associated protein; when it is hyperphosphorylated, its binding affinity to microtubules decreases [126] and, thus, NFTs, a main hallmark of LOAD brains, are formed [120, 127–130]. Therefore, *GSK3B* upregulation as a consequence of hsa-miR-132-3p downregulation could be a relevant process for LOAD development.

Secondly, longevity pathway is overrepresented among the predicted target genes of hsa-miR-212-3p and hsa-miR-132-3p. Both miRNAs are downregulated in LOAD patients, which would lead to the overexpression of their target genes. Alzheimer is a well-known age-related disorder; thus, longevity process was expected to have a main function and to be altered in patients.

In addition, insulin pathway is enriched among the predicted targets of hsa-miR-16-5p and hsa-miR-107, which are downregulated in LOAD patients. Several articles have focused on the putative relationship between insulin pathway and LOAD, pointing to the existence of alterations in insulin signaling in the LOAD brain, which can be both a cause and consequence of LOAD [131, 132]. In fact, many studies have shown that LOAD brains present resistance to insulin [133–136], and there is substantial evidence that brain insulin resistance can increase Aβ and tau, which would promote LOAD development [133, 137–139]. Additionally, it was hypothesized that this insulin resistance in brain could trigger oxidative stress, inflammation, neuronal cell death, etc. [140, 141]. Therefore, changes in the regulation of this pathway, via changes in miRNA expression, could contribute to the development of LOAD, which would be an additional plausible explanation for the role of miRNAs in LOAD.

Finally, MAPK signaling pathway is overrepresented among the predicted target genes of hsa-miR-125-5p and hsa-miR-16-5p. This pathway is mainly related to cell cycle, apoptosis, or inflammation, processes of relevance for LOAD development,, which could explain the role of those miRNAs in the disease. In fact, previous studies have concluded that alterations in MAPK signaling pathways are essential for the development of some AD symptoms, such as neuroinflammation and tau hyperphosphorilation [142]. Target genes of hsa-miR-125-5p are mainly represented in a subpathway responsible for anti-apoptotic processes. Therefore, if genes such as *NFATC3*, *MAPK8*, *PLA2G2A*, or *MAX* are repressed by hsa-miR-125-5p upregulation, apoptosis would be increased. Alternatively, hsa-miR-16-5p is downregulated in LOAD patients, which implies an overexpression of its targets in this pathway, such as Ras or NF-κB, the upregulation of both having been previously related to AD development [143, 144]. On the one hand, earlier studies of Ras levels in AD neurons concluded that an increased expression of Ras leads to phosphorylation of APP and tau, which is associated with Aβ levels in AD brains [144]. On the other hand, NF-κB, has been reported to induce neuroinflammation in the CNS of neurodegenerative diseases in animal models and in patients [143, 145]. In addition, NF-κB activation has been linked to Aβ-induced neurotoxicity [146], further connecting this pathway to LOAD [147]. All of this together could explain the role of those miRNAs in LOAD.

Circulating miRNAs

We considered the studies analyzing circulating miRNAs, with the aim of identifying miRNAs that could be used as non-invasive biomarkers of LOAD, alone or in combination with traditional markers [148]. However, none of the miRNAs presented the same regulation status in four or more articles, which could be a result of the limited number of studies analyzing the same miRNAs and the heterogeneity in sample sources among studies.

Therefore, we focused on the seven miRNAs that were identified as deregulated in brain tissues of LOAD patients.

On the one hand, some miRNAs did not seem to be good markers in circulating tissues, i.e., hsa-miR-34a-5p, which presented contradictory results among studies [60, 65, 72, 98, 100, 111], and hsa-miR-16-5p, which seems to be unchanged in circulating samples of LOAD patients [42, 69, 75]. Furthermore, one of the most consistent miRNAs in brain tissues, hsa-miR-212-3p, has not been studied in liquid tissues to date. Thus, the study of this miRNA would be of great relevance.

On the other hand, we observed that hsa-miR-107, hsa-miR-132-3p, hsa-miR-125-5p, and hsa-miR-181-5p showed a certain potential and could be useful as biomarkers of LOAD in circulating tissues. hsa-miR-107 was measured in 6 different studies [60, 65, 68, 86, 95, 108] and it was

downregulated in three out of the four studies analyzing blood-derived tissues but not in the two studies carried out in CSF. By contrast, hsa-miR-132-3p, hsa-miR-125-5p, and hsa-miR-181-5p only mirrored the results obtained in the brain tissues in CSF and not in blood-derived tissues. First, hsa-miR-132-3p was downregulated, as in brain tissue, in the only studies performed in CSF and serum, respectively, while the study performed in plasma showed a contradictory upregulation [112], further studies are required. Second, hsa-miR-181-5p was found downregulated in only two out of five studies performed in blood-derived samples, while it was downregulated in most studies (three out of four) [60, 65, 99] which analyzed this miRNA in CSF, replicating the result obtained in brain tissues. Lastly, hsa-miR-125-5p family was widely studied in fluid samples, the results showing different regulation status between CSF and blood. Blood-derived samples showed mainly an unchanged status for the miRNA, while it was mainly upregulated in CSF, especially when only hsa-miR-125a-5p was considered, which showed no contradiction among studies [60, 65]. These promising results warrant the need for more studies to identify accurate non-invasive biomarkers of LOAD.

Finally, both categories, studies in non-circulating and circulating tissues, were analyzed together in order to identify miRNAs that could have been studied in a more limited set of studies but that showed consistent results. This way, we observed that all results of hsa-miR-455-3p agree on its upregulation [24, 28]. By contrast, other miRNAs such as hsa-miR-191-5p and hsa-miR-495-3p were concluded as downregulated [27, 103, 107]. Since these miRNAs were analyzed in a limited number of studies, this implies the need to perform additional large scale studies to confirm these results and identify new markers of the disease.

Several limitations were faced while performing this systematic review. A determinant limitation of this study was the heterogeneity in sample source among studies. Additionally, in this review, neighboring brain areas were unified into larger categories in order to be able to compare the data. Different specimen types can set up a wide range of effects on miRNA concentrations and this biological variance may play an important role in clinical utility [10]. Furthermore, LOAD diagnosis was a key limitation, specifically on studies performed in circulating tissues. Unequivocal AD diagnosis is based on a scale that considers brain affectation, which is measured by mediating a histopathological brain autopsy [149]. In the studies in which patients were alive, though, LOAD was diagnosed trusting neurological tests (Mini-Mental State Exam (MMSE), Mini-Cognitive, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, or Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)) [150, 151]. Different tests and ranges of punctuation were found among articles, which may have had an impact on the results obtained, implying difficulties in conclusion extraction. Furthermore, miRNA detection is a complex process that can be affected by technical variability such as collection and storage, miRNA extraction protocol, detection platforms, or normalization [152]. Since the effect of such differences is difficult to determine in the context of a review, it would be of great relevance to reach a consensus and standardize the methodology of study used for future studies in order to facilitate reproducibility and comparisons among studies.

Additionally, most studies analyzed a limited number of miRNAs by qRT-PCR or array, which could underestimate the effect of other miRNAs that might be involved in LOAD. Using methods such as next-generation sequencing (NGS) could help in identifying a larger range of miRNAs, including those that had not been previously described. Furthermore, it is possible that some additional results have been missed because of tendency to only publish statistically significant results, which may lead to a bias. All of these limitations may contribute to lack of consistency in many of the results, which makes it difficult to draw final conclusions about the role of some of the miRNAs analyzed as biomarkers in LOAD. Finally, we have to take into account the inaccuracy of the prediction algorithms of the databases used to determine the target gene and pathways but nowadays this limitation has to be assumed.

Conclusions

Deregulation in brain tissue of seven miRNAs, hsa-miR-16-5p, hsa-miR-34a-5p, hsa-miR-107, hsa-miR-125-5p, hsa-miR-132-3p, hsa-miR-181-5p, and hsa-miR-212-3p, has been consistently identified in LOAD patients. Their role in the disease could be mediated by their putative role in the regulation of key pathways, such as axon guidance, longevity, insulin, and MAPK signaling. Despite the consistent results regarding non-circulating miRNAs as putative LOAD biomarkers, the results regarding circulating miRNAs are more limited and heterogeneous. In this context, preliminary results have shown that the expression of some of those miRNAs, such as hsa-miR-125-5p, hsa-miR-132-3p, and hsa-miR-181-5p, in CSF could serve as a biomarker of LOAD. However, further homogeneously performed studies are required to establish a reliable relationship between miRNAs' expression in fluids and LOAD. This knowledge could allow the identification of better diagnostic markers for LOAD.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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