THE RELATIONSHIP OF RETROELEMENTS WITH microRNAs IN MEMORY FORMATION

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Abstract. Retroelements occupy 37% of the human genome and are involved in the regulation of gene expression in cis and in trans. A number of studies have shown that activation of retroelements in neuronal stem cells of the brain contributes to the genomic mosaicism required for the phenotypic diversity of differentiating neurons. These processes occur in the hippocampus, where memory is also formed, so I have proposed a hypothesis according to which retroelements are drivers of memory formation mechanisms. This is due to the sensitivity of retroelements to environmental influences and their ability to transpose into specific loci of the genome with the activation of brain-specific genes. In addition, proteins and non-coding RNAs involved in memory formation evolved from retroelements. The results of experimental articles are presented that prove this hypothesis, as well as refuting the key role of synaptic plasticity in memory consolidation. The cause of aging and neurodegenerative diseases with memory impairment is the pathological activation of retroelements, which can be influenced by specific microRNAs complementary to these retroelements. Therefore, I analyzed scientific articles in Scopus, Wos, PubMed and the MDTE DB database, which made it possible to identify 33 RE-derived microRNAs involved in Alzheimer's disease, of which 14 are associated with aging, and mechanisms of influence on the brain are described for 18 microRNAs. These microRNAs can be used as tools to target pathologically activated retroelements in aging and Alzheimer's disease to improve memory.

Keywords: microRNA, transposable elements, memory, retroelements, epigenetic mechanisms.

List of Abbreviations

AD – Alzheimer's disease
BDNF – brain-derived neurotrophic factor
DNMT – DNA methyltransferase
ERV – endogenous retrovirus
HDAC – histone acetyltransferase
HERV – human endogenous retrovirus
LINE – long interspersed elements
LTP – long-term potentiation
LTR – long terminal repeats
MDTE DB – microRNAs derived from transposable elements database
miR – microRNA
NSCs – neuronal stem cells
nvRNAs – non-coding RNAs
REs – retroelement
SINE – short interspersed elements
SP – synaptic plasticity
SVA – SINE-VNTR-Alu

Introduction

Retroelements (REs) belong to the first class of transposable elements. They move within the genome using a cut-and-paste mechanism. The enzymes necessary for this, reverse transcriptase and endonuclease, are encoded in autonomous REs genes, which can contain long terminal repeats (LTR-REs), or not contain them – nonLTR-REs. Autonomous nonLTR-REs include LINE (Long Interspersed Elements), non-autonomous ones include SINE (Short Interspersed Elements) and SVA (SINE-VNTR-Alu) (Mustafin & Khusnutdinova, 2018). Retroelements make up a significant part of the human genome. LTR-REs occupy 10% of the human genome, LINE1 – 17%, SINE1 – 10% (Sankowski *et al.*, 2019). The evolutionary domestication of REs has resulted in the origin of many protein-coding genes (Feschotte, 2008), non-coding RNAs (ncRNAs) such as long ncRNAs (Johnson & Guigo, 2014) and microRNAs (Wei *et al.*, 2016), transcription factors and binding sites for them (Mustafin, 2019). Therefore, REs have a global regulatory effect on gene expression in ontogenesis in cis and in trans, which is manifested by their programmed activation during the differentiation of specific cells (Mustafin & Khusnutdinova, 2018).

The highest RE activity was detected in the dentate gyrus of the hippocampus (the center of neurogenesis in humans and experimental animals). In this area, active translocations of

LINE1 have been described in rat neuronal stem cells (NSCs) and have been proposed as drivers of NSC differentiation into various types of neurons in connection with the formation of somatic mosaicism (Muotri *et al.*, 2005). In human brains, two independent studies also showed movements of LINE1 in NSCs (Coufal *et al.*, 2009, Baillie *et al.*, 2011). In humans, genome-wide profiling of Alu and LINE1 genomic DNA from different tissues showed the highest RE activity in the dentate gyrus of the hippocampus (Kurnosov *et al.*, 2015), in which the number of new LINE1 insertions per cell averaged 13.7. Transpositions were found near genes necessary for the functioning of neurons, which indicates the influence of these insertions on cells functioning (Upton *et al.*, 2015). At the same time, hippocampus plays a key role in learning and memory formation (Zhang *et al.*, 2021a), which suggests the role of REs as drivers of these processes. Indeed, it has been proven that in adult human brain, the triggers for RE expression in hippocampal cells are various environmental factors, such as stress (Ponomarev *et al.*, 2010; Hunter *et al.*, 2012), physical exercise (Muotri *et al.*, 2009), methamphetamine (Moszczynska *et al.*, 2015) and alcohol use (Ponomarev *et al.*, 2012).

Since many long ncRNAs (Johnson and Guigo, 2014) and microRNAs (Wei *et al.*, 2016) have evolved from REs, activation of REs may be reflected in the gene expression of these ncRNAs. Indeed, ncRNAs are abundantly and specifically expressed in mammalian brain. RNA sequencing analysis with induction of long-term potentiation (LTP) in the dentate gyrus of living rats 30 minutes, 2 hours and 5 hours after high-frequency stimulation of the perforant tract showed a positive and significant correlation of the dynamic expression of long ncRNAs with protein-coding genes and LINE1 and SINE retroelements (Maag *et al.*, 2015). About 70% of all microRNAs are expressed in the brain, and each region is characterized by a specific miRNA activation pattern (Chen & Qin, 2015). In hippocampal neurons, Dicer induction by BDNF leads to enhanced synthesis of miR-7a, -7b, -7f, -9, -107, -124a, -125b, -132, -134, -143, -375 (Leal *et al.*, 2014). According to a systematic review of the scientific literature, during memory consolidation, the expression of miR-124, miR-134, miR-206 is activated to the greatest extent, and the levels of miR-9-3p, miR-92, miR-195, and the miR-183/96/182 cluster are reduced (Grinkevich, 2020).

It can be assumed that the formation of memory in the human brain occurs due to the activation of REs in specific neurons and during their maturation from NSCs, since REs are highly sensitive sensors of environmental influences (Ponomarev *et al.*, 2010; Hunter *et al.*, 2012; Muotri *et al.*, 2009; Moszczynska *et al.*, 2015; Ponomarev *et al.*, 2012). Since REs are drivers of epigenetic regulation in ontogenesis (Mustafin & Khusnutdinova, 2017), this is reflected in the expression of specific genes in the brain due to the influence of epigenetic factors. Neurotransmitter genes involved in the dopaminergic system: *DAT1, DRD4, CNR1* (Leukel *et al.*, 2020) and glutamatergic system: NR2B (encodes a subunit of the inotropic glutamate receptor N-methyl-d-aspartate) (Noyes *et al.*, 2021) play a role in the consolidation of long-term memory. The association of *CTNNB1* (beta-catenin) (Tan *et al.*, 2013), *CREB* (cAMP-responsive element binding protein) (Hegde & Smith, 2019), *NF-κB* (Kaltschmidt & Kaltsmidt 2015), *Zif268, XBP1, Srf, Npas4, Foxp1, Crtc1, c-Rel* (Hegde, Smith, 2019) genes with memory formation was identified. Memory suppressor genes, which include *AIM2, ATF4, BChE, Bec1, CCR5, Cdk5, crtl1, Diap1, Dicer1, DFF45, GABAaB3, GABAARα4, Gabra 4, Galectin-3, GAT1, QR2, np65, Hcn1, Hdac2, Mef2, Kvβ1.1, PDE1b, Paip2a, Pkr, GCN2, IRS2, RGS14, RARalpha, p75NTR, PDE4A, Ogg1, PERK, RPTPsigma, Piwi1, Piwi2, S100b, TLCN, Pde4d, Pde8b, 11b-HSD1* (Noyes *et al.*, 2021) also play a role in memory consolidation. Since miRNAs inhibit gene expression, it is promising to determine the epigenetic effects of miRNAs on these genes to improve memory.

Epigenetic factors, in addition to ncRNAs, include DNA methylation and histone modifications (H2BK120ub, H3K9me2, H3K36me3,

H3K27me3, H3K9me3, H3K4me3, H3K14ac, H3K9ac influences memory formation) (Hegde & Smith, 2019). DNA methylation and histone modifications at specific loci depend on the influence of microRNAs, which are guides that recognize complementary sequences not only of mRNA, but also of DNA molecules in the mechanism of RNA-dependent DNA methylation (Chalertpet *et al.*, 2019). Therefore, REs may serve as the primary drivers causing epigenetic changes during memory formation, since ncRNAs originate from them (Johnson, Guigo, 2014; Wei *et al.*, 2016) or are formed directly from REs transcripts (Honson & Macfarlan, 2018; Lu *et al.*, 2014). A number of scientific works provide data confirming this assumption.

Confirmation of the role of retroelements in memory formation

Experiments on mice have shown that exposure to a new environment leads to an increase in the number of double-strand breaks in neurons in different areas of the brain, most often in dentate gyrus of the hippocampus (Suberbielle *et al.*, 2013). The sources of these double-stranded DNA breaks can be REs during their transposition into new genomic loci (Yenerall & Zhou, 2012) which suggests their role in the reactions of hippocampal cells to environmental influences with memory formation. Experiments in mice on inhibition of LINE1 in the hippocampus revealed the role of REs in memory consolidation through genomic mosaicism. To do this, mice were placed on the illuminated side, after which they were allowed to move to the dark side of the chamber, where they received an electric shock. The learning memory was reflected in an increase in mouse latency when moving to the dark side of the chamber. 72 hours after administration of lamivudine (which inhibits LINE1 reverse transcriptase) to the hippocampus, memory was significantly impaired (Bachiller *et al.*, 2017). Studies have also been conducted in mice on the reconsolidation of context-sensitive fear memory. Fear memory was assessed in observation chambers by measuring the percentage of time spent freezing for 5 minutes, and hippocampal and prefrontal cortex samples were used for quantitative RT-PCR of LINE1 transcripts. The results revealed LINE1 expression in the hippocampus and prefrontal cortex during fear memory. After reactivation of the fear memory, lamivudine was administered; reconsolidation of the fear memory was markedly suppressed due to inhibition of LINE1 (Zhang, 2021).

RE transpositions occur among memory-associated neurons in the Drosophila brain, which express the piRNA-interacting proteins Aubergine and Argonaute-3, which suppress REs (the loss of these proteins correlates with RE activation in the brain). Deep sequencing of individual neurons reveals more than 200 de novo RE insertions in memory-related neurons (Perrat *et al.*, 2013). According to the ENCODE and FANTOM consortia, RE activity depends on the cell type and affects neighboring genes expression. REs are of greatest importance in brain regulating, in which, compared to other tissues, the largest number of somatic retrotranspositions is found. These RE retrotranspositions provide various adaptive functions of the central nervous system. In response to the effects of steroids, epigenetic and environmental factors, they change the functioning of neurotransmitter systems to adapt to changing environmental conditions (Lapp & Hunter, 2016).

RE insertions play a regulatory role not only for NSCs, but also in the late phase of neuronal differentiation (Muotri *et al.*, 2010). As a result, specific pattern of gene expression is formed in neurons located in certain areas of the brain, due to which memory is formed (Singer *et al.*, 2010). SINEs in the mouse hippocampus are characterized by cell type-specific expression profiles. Moreover, in response to short-term exposure of animals to a novel stimulus, SINEs were activated in dentate granule neurons over a time course similar to that of protein-coding genes (Linker *et al.*, 2020). In human U251 glioma cells, increased expression of the HERV-w retroelement env gene activated BDNF (brain-derived neurotrophic factor) (Huang *et al.*, 2011), which plays an important regulatory role in synaptic transmission and LTP in the hippocampus and other brain regions to form various forms of memory. BDNF effects are mediated by tropomyosin-related kinase-B

(TrkB) receptors, which are associated with activation of phospholipase C-γ, phosphatidylinositol 3-kinase, and Ras/ERK pathways. BDNF protein regulates the transport of mRNA along dendrites and their active translation in synapses, modulating the initiation and elongation phases of protein synthesis and affecting specific microRNAs (Leal *et al.*, 2014).

Although activation of RE is normally the basis for memory formation, their pathological expression can cause its impairment and the development of neurodegenerative diseases. Therefore, the reverse transcriptase inhibitor lamivudine in experiments on P301S mice (modeled for Alzheimer's disease) reduced histopathological signs typical of tauopathies: tau phosphorylation, inflammation, neuronal death, hippocampal atrophy. Lamivudine alleviated motor impairment and improved short-term memory. The ability of lamivudine to suppress LINE1 insertions was demonstrated in HeLa cell lines (Valles-Saiz *et al.*, 2023). The role of ERVs in memory consolidation is evidenced by experimental studies in mice lacking the mitochondrial antiviral signaling protein MAVS for the interferon gene stimulator STING. These animals showed an increase in ERV expression, accompanied by a significant change in hippocampal-associated memory (Sankowski *et al.*, 2019).

The assumption of REs role in memory formation is supported by studies that refute the importance of synaptic plasticity (SP) in these mechanisms. Previously, it was believed that the SP ensures information storage and memory consolidation in the brain. This requires rapid synthesis of mRNA in the nucleus and proteins in synapses (Fila *et al.*, 2021), and LTP of synaptic transmission is considered a cellular mechanism for learning and memory storage (Maag *et al.*, 2015). However, a number of experiments have shown memory consolidation without the participation of the SP. Back in 1984, an experiment on *Manduca sexta* revealed memory retention of the need to avoid a specific odor during metamorphosis with the reorganization of synapses. This memory was formed at the caterpillar stage and was determined in mature moths, despite the reorganization of dendritic morphology and changes in the relationships between neurons (Levine, 1984). The memory of recognizing a textured surface to determine the presence of food was retained in planarians after removal of the head and subsequent regeneration of the brain with complete restoration of new synapses (Shomrat & Levin, 2013). In a coculture of motor and sensory neurons from the sea hare *Aplysia*, long-term memory for training with interval serotonin pulses was latently preserved after its apparent elimination by anti-mnemonic drugs that erase learning-associated synaptic growth (Chen *et al.*, 2014). In experiments in mice, the restoration of fear memory was determined when engram cells were reactivated in the absence of synaptic changes (after administration of the protein synthesis inhibitor anisomycin) (Ryan *et al.*, 2015).

Since REs are drivers of epigenetic regulation of gene expression (Mustafin & Khusnutdinova, 2017), activation of REs during memory formation in the hippocampus and other areas of the brain (Bachiller *et al.*, 2017; Perrat *et al.*, 2013; Zhang *et al.*, 2021a) naturally affects chromatin changes in these processes. This is also due to the influence of RE-derived microRNAs on histone modification enzymes (Mustafin & Khusnutdinova, 2017) and the use of microRNAs as guides for DNA methylation in specific genome regions (Chalertpet *et al.*, 2019). Indeed, chromatin modifications are an integral part of learning and memory, and changes in the activity of enzymes affecting them affect the cognitive abilities of humans and animals (Halder *et al.*, 2016). Exposure to DNA methyltransferase (DNMT) inhibitor disrupted fully consolidated fear memory 1 month after contextual fear maintenance in rats (Miller *et al.*, 2010). Memory consolidation in mice required changes in chromatin modification in neurons and other brain cells (Halder *et al.*, 2016).

Enhancing histone acetylation by manipulating the activity of a specific isoform of histone acetyltransferase (HDAC) and DNMT in neurons limited memory consolidation (Jarome & Lubin, 2014). REs can participate in memory formation not only due to their regulatory influ-

ence on the expression of specific genes in neurons by in cis and in trans mechanisms, but also due to the direct participation of their transcription and translation products in these mechanisms. For example, LTR-REs can directly serve as genes for long ncRNAs (Lu *et al.*, 2014). LINE1 transcripts function as lncRNAs that interact with specific regions of chromatin and regulate expression (Honson & Macfarlan, 2018). The use of REs expression products in memory regulation is evidenced by the domestication of their proteins for these purposes in evolution.

The role of proteins derived from retroelements in memory formation

According to a scientific article published in 2016 citing the MDTE DB database, 661 human microRNAs originated from transposable elements, mainly from REs (Wei *et al.*, 2016). The origin of protein-coding genes in evolution from REs may explain the presence of nucleotide sequences similar to them in microRNAs that inhibit these genes expression. According to results of the analysis published in 2008, REs in evolution were sources of various proteins in eukaryotes, including humans. Some of these proteins are involved in memory formation (Feschotte, 2008). The myelin basic protein transcription factor MyEF-3 gene is expressed in the brain, regulating its development (Steplewski *et al.*, 1998). This protein evolved from the Gag protein of Gypsy-like retroelements (Volff, 2006; Alzohairy *et al.*, 2013). The ERV Gag protein gave rise to the PEG10 protein, which interacts with ATXN2 and ATXN10 in stress granules and extracellular vesicles and affects neuronal migration during memory formation (Pandya *et al.*, 2021). The CCNS type of zinc finger protein also evolved from the ERV Gag protein. Deletion of the *SIRH11/ZCCHC16* gene encoding this protein in experiments on mice causes abnormal behavior associated with cognitive abilities, including working memory (Kaneko-Ishino & Ishino, 2016).

The phosphoprotein genes ma-1/map-1, ma-3, expressed in the brain, originated from GAG retroelements Ty3/Gypsy (Volff, 2006; Alzohairy *et al.*, 2013). The source of the *RTL1* (Retrotransposons Gag like 1)/*PEG11* (Paternally expressed gene 11) gene in evolution was the Gag gene of endogenous retroviruses. *RTL1/PEG11* gene is characterized by imprinting of the maternal allele with expression in the placenta and during embryonic development. In the postnatal period, the *RTL1/PEG11* gene is expressed in the brainstem, locus coeruleus, thalamus and hypothalamus. In mice with knockout of the paternal allele (Rtl1m+/p-), a decrease in the excitability of neurons in the locus coeruleus, as well as anxious and depressive behavior, impaired learning, social dominance and memory were determined (Chou *et al.*, 2022).

The Prp8 protein, which is a component of the eukaryotic spliceosome, evolved from ERV reverse transcriptase (Dlakic & Mushegian, 2011). Experiments on Drosophila demonstrated the key role of Pp8 in controlling the expression of FMRFa neuropeptide in neurons (Cobeta *et al.*, 2018). The TERT protein, derived from REs reverse transcriptase (Kopera *et al.*, 2011), regulates spatial memory formation by modulating neuronal development in the hippocampus (Zhou *et al.*, 2017). The Arc protein (Activity-regulated cytoskeleton-associated protein) regulates SP in the control of signaling networks during learning, behavior and memory consolidation. *Arc* gene transcripts are transported to dendrite synapses, where protein is synthesized from them on ribosomes (Ashley *et al.*, 2018; Pastuzyn *et al.*, 2018). In 2006, computer analysis showed that the Arc gene in humans originated from the Ty3/gypsy RE (Campillos *et al.*, 2006). Phylogenetic analysis confirmed these results. Arc has been shown to form a capsid that encapsulates its own mRNAs. The resulting virus-like structures are loaded into extracellular vesicles and transported to neurons, transmitting genetic information and regulatory signals through neural networks, which is necessary for memory formation (Ashley *et al.*, 2018; Pastuzyn *et al.*, 2018).

The relationship of retroelements with microRNAs in memory pathology

Prospects for studying the role of REs in memory formation are associated with the possibility of improving cognitive abilities during

aging (since mobile genetic elements are important regulators of this process (Gorbunova *et al.*, 2021)) and for the treatment of brain diseases with memory impairment, such as Alzheimer's disease (AD) (Lugli *et al.*, 2015; Sierksma *et al.*, 2018). The importance of REs in AD development determined in a number of scientific works. In experiments on mice modeled for AD by knocking out one allele of the Bmi1 gene, the development of neurodegeneration due to REs derepression was shown (El Hajjar *et al.*, 2019). Enhanced processing of non-coding RNAs from SINE B2 transcripts in the hippocampus under the influence of amyloid deposition was revealed (Cheng *et al.*, 2020). It has also been shown that G-quadruplex, derived from the evolutionarily conserved L1, suppresses gene expression in AD neurons (Hanna *et al.*, 2021). Transcriptomic analysis revealed aging- and tau-induced ERV activation in mouse brain. In mice transgenic for the expression of tau protein, an increased number of REs copies was determined in the brain (Ramirez *et al.*, 2022b). Analysis of postmortem brain tissue samples showed that in tauopathies, decondensation of heterochromatin and a decrease in the levels of piwi and piRNA cause deregulation of REs. In AD patients, a significant increase in the amount of HERV transcripts was found (Sun *et al.*, 2018), with differential expression of several specific REs in association with the load of neurofibrillary tau tangles (Guo *et al.*, 2018), as well as activation of specific LINE1 and Alu (Grudman *et al.*, 2021). According to the analysis of blood samples from late-onset AD patients, before clinical phenoconversion (from normal cognitive indicators to the manifestation of AD), an REs storm occurs - increased expression of 1790 different LINE, LTR, SVA (Macciardi *et al.*, 2022). The data obtained confirm the key role of REs in memory formation, since the normal functioning of the brain requires the expression of specific REs. During aging and neurodegenerative processes, pathological activation of REs occurs, which is reflected in the impairment of cognitive processes, including memory, as well as in the expression of specific microRNAs. To control the activity of REs, it is possible to use ncRNAs derived from them, which in the future may become the basis for targeted therapy for AD and slowing down the aging process of the brain.

I analyzed the literature data on the role of microRNAs derived from transposons (Wei *et al.*, 2016) in the development of AD and aging (Table 1). Increased levels of miR-1202 (Henriques *et al.*, 2020), miR-1246 (Guo *et al.*, 2017b), miR-151 (Satoh *et al.*, 2015), miR-211 (Sierksma *et al.*, 2018) have been identified in AD. Expression of miR-1202 was detected in neuroglial cells. The target of this microRNA is *Rab1a* gene mRNA, due to which miR-1202 suppresses the TLR4/NFκB inflammatory signaling pathways (Song *et al.*, 2020). Low expression of miR-151 was detected during aging (Noren Hooten *et al.*, 2013). In the brain, miR-151 inhibits the expression of *APH1a* gene mRNA, affecting contextual memory formation (Xu *et al.*, 2019). Microarray analysis showed that miR-211 is involved in the regulation of neuronal migration and differentiation (Mainigi *et al.*, 2016). An experiment on mice modeled for AD confirmed the role of miR-211 dysregulation in the development of the disease and the involvement of this microRNA in neurons formation (Li *et al.*, 2021). Increased levels of miR-211 were also detected during aging (Smith-Vikos *et al.*, 2016).

AD is characterized by low expression of miR-1271 (the target is the mRNA of the tyrosine kinase receptors ALK and RYK in the brain (Majumder *et al.*, 2021)). A study of AD patients, of whom 45 subjects cycled continuously for 3 months, showed changes in miR-192-5p expression before and after exercise, which contributed to cognitive improvements (Qin *et al.*, 2022). Low levels of this microRNA are also associated with aging (Sataranatarajan *et al.*, 2012). miR-192 expression restores cognitive impairment and neural function via Fbln2-mediated TGF-β1 signaling pathway (Tang *et al.*, 2019).

In mice model of AD, an increased level of miR-28-3p was detected in the cerebrospinal fluid (Hong *et al.*, 2017) and in the blood serum of people with AD (Zhao *et al.*, 2020). Low levels of this microRNA are associated with aging

Table 1

Specific microRNAs expression changes in Alzheimer's disease and aging

N	miRNA	RE – source of miRNA	microRNAs expression change in Alzheimer's disease (author) (↑ – increase, ↓ – decrease)	microRNAs expression change in aging (author) (↑ – increase, ↓ – decrease)	Regulation of brain functioning by microRNAs (author)
1	miR-1202	LINE1	↑ (Henriques *et al.*, 2020)		(Song *et al.*, 2020)
2	miR-1246	ERVL	↑ (Guo R. *et al.*, 2017)		
3	miR-1271	LINE2	↓ (Majumder *et al.*, 2021)		(Majumder *et al.*, 2021)
4	miR-151	LINE2	↑ (Satoh *et al.*, 2015)	↓ (Noren Hooten *et al.*, 2013)	(Xu *et al.*, 2019)
5	miR-192	LINE2	↓ (Qin *et al.*, 2022)	↓ (Sataranatarajan *et al.*, 2012)	(Tang *et al.*, 2019)
6	miR-211	LINE2	↑ (Sierksma *et al.*, 2018; Li *et al.*, 2021)	↑ (Smith-Vikos *et al.*, 2016)	(Mainigi *et al.*, 2016)
7	miR-28	LINE 2	↑ (Hong *et al.*, 2017; Zhao *et al.*, 2020)	↓ (Zhang *et al.*, 2017)	
8	miR-31	LINE2	↓ (Barros-Viegas *et al.*, 2020)	↓ (Shan *et al.*, 2017)	(Qian *et al.*, 2022)
9	miR-3199	LINE2	↓ (Sun *et al.*, 2022)		
10	miR-320c	LINE2	↑ (Raheja *et al.*, 2018; Boese *et al.*, 2016)	↓ (Ukai *et al.*, 2012)	
11	miR-3200	ERV-L	↓ (Satoh *et al.*, 2015)		
12	miR-325	LINE2	↓ (Barak *et al.*, 2013)		(Barak *et al.*, 2013)
13	miR-335	SINE	↑ (Bottero and Potashkin, 2019)	↑ (Raihan *et al.*, 2018)	(Capitano *et al.*, 2017)
14	miR-342	SINE	↓ (Dakterzada *et al.*, 2021)		(Dong *et al.*, 2022)
15	miR-3646	SINE	↑ (Lu *et al.*, 2021)		
16	miR-378a	SINE	↑ (Dong *et al.*, 2021)	↑ (Guo *et al.*, 2017)	(Weng *et al.*, 2023)
17	miR-384	LINE/Dong-R4	↑ (Samadian *et al.*, 2021)		(Gu *et al.*, 2015)
18	miR-4286	LTR/ERVL	↓ (Henriques *et al.*, 2020)		
19	miR-4422	LTR/Gypsy	↓ (Hajjri *et al.*, 2020)		
20	miR-4487	LINE1	↓ (Hu *et al.*, 2018)	↓ (Wang *et al.*, 2021)	(Hu *et al.*, 2018)
21	miR-4504	LINE1	↑ (Eysert *et al.*, 2021)		(Eysert *et al.*, 2021)
22	miR-4772	LINE1	↓ (Lugli *et al.*, 2015)		
23	miR-502	LINE2	↓ (Satoh *et al.*, 2015)		
24	miR-511	LINE1	↓ (Wang *et al.*, 2023)	↓ (Zheng *et al.*, 2016)	(Zheng *et al.*, 2016)
25	miR-545	LINE2	↓ (Cosin-Tomas *et al.*, 2017)		
26	miR-566	SINE/Alu	↑ (Yaqub *et al.*, 2023)		
27	miR-576	LINE1	↓ (Liu *et al.*, 2014; Xu *et al.*, 2022)	↑ (Ipson *et al.*, 2018)	
28	miR-6087	LINE1	↓ (Lau *et al.*, 2013)		
29	miR-619	LINE1	↓ (Baek *et al.*, 2021)		(Baek *et al.*, 2021)

End of table 1

N	miRNA	RE – source of miRNA	microRNAs expression change in Alzheimer's disease (author) (↑ – increase, ↓ – decrease)	microRNAs expression change in aging (author) (↑ – increase, ↓ – decrease)	Regulation of brain functioning by microRNAs (author)
30	miR-659	LINE2	↓ (Lugli *et al.*, 2015)		(Pisopo *et al.*, 2016)
31	miR-664	LINE1	↓ (Schonrock *et al.*, 2010)	↑ (Lee *et al.*, 2017)	(Ju *et al.*, 2019)
32	miR-708	LINE2	↓ (Rahman *et al.*, 2020; Di Palo *et al.*, 2022)	↑ (Lee *et al.*, 2017)	(Vatsa *et al.*, 2019)
33	miR-885	SINE/MIR	↓ (Tan *et al.*, 2014)	↑ (Behbahanipour *et al.*, 2019)	(Pan *et al.*, 2022)

(Zhang *et al.*, 2017). MiR-31 inhibits beta-amyloid formation and improves cognition by targeting APP and BACE1 in AD mice model (Barros-Viegas *et al.*, 2020). miR-31 expression is significantly reduced in the hippocampus and prefrontal cortex of aged rats compared to young controls (Shan *et al.*, 2017). This microRNA inhibits apoptosis of nerve cells by regulating hypoxia-inducible factor-1A/vascular endothelial growth factor A axis (Qian *et al.*, 2022). Bioinformatic analysis of the microRNA regulatory network in AD showed the participation of miR-3199 in this network (Sun *et al.*, 2021).

Increased expression of miR-320c was detected in AD patients (Raheja *et al.*, 2018) and AD model mice (Boese *et al.*, 2016). Low levels of this microRNA are associated with aging (Ukai *et al.*, 2012). In AD, decreased expression of the microRNA miR-3200 was also determined (Satoh *et al.*, 2015). AD is characterized by reduced expression of miR-325, which has a post-transcriptional regulatory effect on tomosyn synthesis (impairs synaptic transmission in the brain) in the hippocampus (Barak *et al.*, 2013). A meta-analysis of changes in gene expression in the blood of AD patients showed the specificity of a high level of miR-335, which is proposed as a biomarker of the disease (Bottero & Potashkin, 2019). Increased expression of miR-335 is also associated with aging (Raihan *et al.*, 2018). miRNA-335 was found to modulate spatial memory and synaptic plasticity in the hippocampus (Capitano *et al.*, 2017).

In AD patients, an association of lower levels of miR-342 with a rapid decline in cognitive function has been identified (Dakterzada *et al.*, 2021). Analysis of circulating small extracellular vesicles in patients identified decreased levels of miR-342, which promoted beta-amyloid formation through beta-site targeting of amyloid precursor protein cleaving enzyme (BACE1) (Dong *et al.*, 2022). Increased expression in AD was determined for miR-3646 (Lu *et al.*, 2021), miR-378a (Dong *et al.*, 2021) и miR-384 (Samadian *et al.*, 2021). High levels of miR-378a are also associated with aging (Guo *et al.*, 2017a). The target of miR-378 is the mRNA of the EZH2 gene (enhancer of zeste homolog-2), which is expressed in brain neuroglia and regulates the production of proinflammatory chemokines and cytokines (Weng *et al.*, 2023). MiR-384 is required for protein synthesis-dependent maintenance of LTP (Gu *et al.*, 2015).

Reduced expression in AD was determined for miRNA-4286 (Henriques *et al.*, 2020), miR-4422 (Hajjri *et al.*, 2020), miR-4487. In experiments on cell lines, miR-4487 reduced beta-amyloid-induced apoptosis in neurons (Hu *et al.*, 2018). MiR-4487 is predicted as a target microRNA interacting with circular RNAs in-

volved in skin aging (Wang *et al.*, 2021). Assessment of the functional influence of genes and microRNAs on APP (Amyloid Precursor Protein) metabolism showed that FERMT2 (Kindlin-2) directly interacts with APP, modulating its metabolism, and miR-4504 suppresses FERMT2 expression (Eysert *et al.*, 2021). Comparative analysis of microRNA expression showed a significant difference in miR-4772 expression in AD patients compared to healthy controls (Lugli *et al.*, 2015). Low levels in AD have been identified for miR-502 (Satoh *et al.*, 2015), miR-511 (Wang *et al.*, 2023), miR-545 (Cosin-Tomas *et al.*, 2017). A decrease in miR-511 expression is also associated with aging. This microRNA binds to mRNA of *FKBP5* gene (encodes a chaperone protein) and regulates neuronal differentiation (Zheng *et al.*, 2016).

Genome-wide profiling of circulating microRNAs in patients with AD showed that miR-566 is associated with dementia in AD (Yaqub *et al.*, 2023). An association of low expression with AD was detected for miR-576 (Liu *et al.*, 2014; Xu *et al.*, 2022), miR-6087 c (Lau *et al.*, 2013), miR-619 (Baek *et al.*, 2021), miR-659 (Lugli *et al.*, 2015), miR-664 (Schonrock *et al.*, 2010), miR-708 (Rahman *et al.*, 2020; Di Palo *et al.*, 2022), miR-885 (Tan *et al.*, 2014). An analysis of the scientific literature showed that increased expressions of miR-576 (Ipson *et al.*, 2018), miR-708 (Lee *et al.*, 2017) and miR-885 (Behbahanipour *et al.*, 2019) are also associated with aging. The targets of miR-619 are the mRNAs of the *PPP1CB, PPP1CC, CREBBP, HELZ2, NCOA1, TBL1X* genes, which are associated with circadian rhythm genes (Baek *et al.*, 2021). The target of miR-659 is the mRNA of the progranulin gene (GRN), which is expressed in the brain (Piscopo *et al.*, 2016). MiR-664 is produced in the brain. In hypothalamic neurons, miR-664 binds to the 3'UTR of the NMDAR1 gene (N-methyl-D-aspartate receptors), which stimulates the secretion of GnRH (Ju *et al.*, 2019). The target of miR-708 in the brain is the reticulum resident protein neuronatin (a developmentally regulated protein in the brain) (Vatsa *et al.*, 2019). The target of miR-885 is KREMEN1, the expression of which is reduced in the brain at elevated levels of miR-885, which attenuates Aβ-triggered cell injury (Pan *et al.*, 2022).

Conclusion

A number of scientific works have obtained experimental evidence refuting the key role of SP in memory consolidation. At the same time, the role of activation and movement of REs to new genomic loci in this process has been proven. REs are sensors of the genome to environmental influences and internal changes, which can explain their participation in the formation of connections between neurons during memory consolidation. The mediators are both direct products of transcription and translation of REs, as well as ncRNAs and proteins derived from REs in the evolution, the role of which in the formation of memory has been described. Since RE play a role in normal memory consolidation, it is logical to assume the significance of pathological activation of RE in neurodegenerative processes with memory impairment. Indeed, an analysis of the scientific literature made it possible to find evidence that in AD, the activity of the REs themselves, as well as the microRNAs derived from them, changes. Analysis of the MDTE DB database revealed 33 such microRNAs, for 18 of which the mechanism of action on genes expressed in the brain was described. In addition, 14 out of 33 identified microRNAs are associated with aging, which indicates the involvement in the pathogenesis of AD of the same REs and microRNAs derived from them, the expression of which changes with aging. The data obtained can be used to target pathologically altered REs in order to improve memory during aging and AD.

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