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Review

Relationship of Retroelements with Antiviral Proteins and Epigenetic Factors in Alzheimer's Disease

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Abstract

Genetic factors such as allelic variants of the PSEN1, PSEN2, APP, and APOE genes play an important role in Alzheimer's disease development. Still, they cannot explain all cases of the disease and cannot form the basis for effective treatment methods for the pathology. Alzheimer's disease is the most common neurodegenerative disease, so identifying new mechanisms of pathogenesis may reveal new ways of treating it. Since Alzheimer's disease is associated with aging, the hypothesis is proposed that an important trigger mechanism for it is the pathological activation of retroelements during aging, leading to epigenetic changes. This is due to the role of retroelements in gene expression regulation and the origin of long noncoding RNAs and microRNAs from transposons, changes in the expression of which are observed both during aging and Alzheimer's disease. Normally, activation of retroelements is observed in hippocampal neuronal stem cells, which is necessary for epigenetic programming during neuronal differentiation. Direct changes in the expression of retroelements in Alzheimer's disease have also been described. It has been suggested that aging is a trigger for the development of Alzheimer's disease due to the pathological activation of retroelements. To confirm this hypothesis, an analysis of specific microRNAs associated with Alzheimer's disease and aging in the MDTE DB (microRNAs derived from Transposable elements) database

was conducted. As a result, identified expression changes in Alzheimer's disease of 37 individual microRNAs derived from retroelements (25 from LINE, 7 from SINE, 5 from HERV), of which 12 changes expression during physiological aging, which confirms my hypothesis that the activation of retroelements during physiological aging is a driver for Alzheimer's disease. This is evidenced by the defeat of diseases mainly by the elderly and older adults. Since 3 of the 12 miRNAs associated with aging and Alzheimer's disease originated from SINE/MIRs that evolved from tRNAs, the role of tRNAs and the tRFs and tRNA halves derived from them in the development of Alzheimer's disease, which are evolutionarily closely related to retroelements was described. These results are promising for targeted disease therapy in the mechanisms of RNA-directed DNA methylation with possible complex use of retroelement enzyme inhibitors. Additional evidence for the role of retroelements in the development of Alzheimer's disease is that overexpression of tau, which has antiviral properties, with its interaction with beta-amyloid leads to dysregulation of retroelements, and in tauopathies, activation of ERV is determined. At the same time, the effect of retroelements as inducers of proteinopathy and tau aggregation has been described. In addition, HIV and herpes viruses, which affect beta-amyloid and tau protein, are also activators of retroelements. Also, polymorphisms associated with Alzheimer's disease are located mainly in intronic and intergenic regions where retroelements are located, affecting changes in their activity.

Keywords
Alzheimer's disease; lncRNA; miRNA; aging; retroelements; transfer RNA

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease characterized by the deposition of beta-amyloid and tau tangles in the brain [1]. Multimeric amyloid beta fibrils form neuritic plaques, and hyperphosphorylated tau proteins form neurofibrillary tangles. As a result, synapses, dendrites, and neurons are lost [2]. Before neurofibrillary tangles develop in the cerebral cortex, neuropathological changes occur in the subcortical nuclei [1]. AD is the most common cause of dementia and affects more than 50 million people worldwide [2]. The association of AD with aging has been proven (Table 1). 18.54% for over 85s in China (1.25% for ages 65-69), 22.53% for over 85s in Europe [3] are affected by this disease. In most cases, AD is a multifactorial disease. However, there are rare cases of monogenic forms of AD with an autosomal dominant type of inheritance due to mutations in the presenilin genes (*PSEN1, PSEN2* - their protein products enhance the formation of beta-amyloid, play a role in autophagy) and amyloid precursor protein (*APP* - from which beta-amyloid is formed in AD) [4, 5].

Table 1 Distribution of AD in aging populations (according to data [3]).

Indicators	Japan	USA	China	Europe	South Korea
average frequency of occurrence worldwide regardless of age	5%	5%	5%	5%	5%
frequency of occurrence in people over 65 years of age	7%	9.51%	1.27%	4.5%	5.7%
frequency of occurrence in people over 85 years of age			18.54%	22.53%	

Genetic factors play an important role in AD development since the heritability of the disease, according to twin studies, is 58% [6]. The most pronounced genetic risk factor for AD is the *APOE* ε4 allele since APOE affects beta-amyloid aggregation and clearance, microglial response, and neurofibrillary changes in tau protein [7]. Allelic variants of the *PSEN1, PSEN2*, and *APP* genes also have an essential influence on the development of AD [5]. Meta-analyses of GWAS results also determined the association of AD with polymorphic variants of many other genes, which include *ABCA7* [8], *BIN1, PICALM* [9], *TREM2* [10], *CR1, APOJ* [11], *MTHFR, BIN1* [12], *APH1B, CASS4, CCDC6, NCK2, PILRA, PTK2B, SPRED2, TSPAN14* [13] genes. However, explaining the involvement of these gene protein products in AD development is challenging. Before explaining the causes, it is vital to make sure if there is involvement at all, as the association does not imply causation because many of the AD-associated polymorphic loci are located in introns or regulatory regions of genes [8-13], where transposable elements (TEs) are located [14]. Indeed, most SNPs associated with multifactorial diseases are localized in intergenic and intronic regions [15], indicating a possible pattern - the influence on the activity of TEs in these regions. A good example is the influence of SNPs located in the ORF1p coding region of the LINE1 (Long Interspersed Nuclear Element 1) retrotroelement (RE), associated with another neurodegenerative disease – amyotrophic lateral sclerosis (ALS). Changes in specific amino acids in ORF1p affect retrotransposition efficiency and protein aggregation dynamics. Proteins that play a crucial role in ALS development are co-localized with ORFp-LINE1 RNP particles in cytoplasmic RNA granules [16]. It can be hypothesized that AD-associated SNPs located in retroelement regions act similarly. Changes in RE activity may similarly affect beta-amyloid and tau proteinopathy. Since TEs are drivers of epigenetic regulation [17], changes in TE activity may be reflected in epigenetic changes in AD pathogenesis.

Epigenetic factors include methylation of specific DNA loci (for example, CpG islands) and histone modifications (methylation, acetylation), which play an essential role in the pathogenesis of AD [18]. In addition, epigenetic factors include RNA interference (RNAi) under noncoding RNAs (ncRNA influence) [19] and pseudouridylation of RNAs by pseudouridine synthase [20]. The name ncRNAs makes it clear that they are not translated but perform their functions as RNA molecules in combination with proteins or independently. NcRNAs are divided into long ncRNAs (lncRNAs - mature molecules contain more than 200 nucleotides) and small ncRNAs (less than 200 nucleotides). Small ncRNAs include transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), rRFs (ribosomal RNA derived fragments), piRNAs (piwi interacting RNAs), snoRNAs (small nucleolar RNAs), snRNAs (small nuclear RNAs, siRNAs (short interfering RNAs), miRNAs (microRNAs) and tRNA derived small RNAs (tsRNAs), which include tRNA fragments (tRFs) and tRNA halves [21].

MicroRNAs in humans regulate gene expression post-transcriptionally (by binding to the 3'-untranslated region (3'-UTR) of mRNA and inhibiting translation [22]) and at the transcriptional level (they are guides for binding DNA methyltransferases to specific loci of the genome using the RNA-directed DNA methylation mechanism) [23]. The primary role of epigenetic factors is to regulate the expression of various genes in a tissue-specific and even cell-specific manner in ontogenesis [24]. MicroRNAs are involved in the development of AD. According to a meta-analysis, the expression of 1915 genes in the hippocampus of the temporal lobe of the cerebral cortex in AD patients differs from healthy people [25]. The hippocampus contains neuronal stem cells characterized by increased activity of RE [26], which are the most important regulators of epigenetic activity in ontogenesis [24]. REs have a regulatory effect *in cis* and *trans* on gene expression, as well as due to the products of processing of their transcripts, which are ncRNA [24, 27].

REs and repeating sequences derived from them occupy 2/3 of the human genome [28]. REs refer to TEs. There are 2 classes of TEs: Class I - retroelements (REs), which transpose by copying RNA into DNA using reverse transcriptase (RT) and inserting it back into the genome at a new locus; Class II - DNA transposons that move by cutting and pasting. REs include containing long terminal repeats (LTR) and not containing them (non-LTR RE). Their transposition mechanisms differ: non-LTR REs cleave DNA targets and trigger reverse transcription using the 3' end. Most LTR-REs in all living organisms use the 3' end of tRNA for reverse transcription priming [29]. Autonomous REs that use self-encoded enzymes for transpositions in the human genome include LINEs (non-LTR REs) and endogenous retroviruses ERVs (LTR-Res, including Human Endogenous RetroViruses - HERVs). Non-autonomous REs use autonomic RE enzymes for their transpositions: non-LTR REs SINE (Short Interspersed Nuclear Elements) and SVA (SINE-VNTR-Alu). SINEs occupy at least 13% of the human genome [30].

The composition and distribution of REs in the genome are a species-specific characteristic. They can serve as a genetic code for controlling gene expression in space and time in the human body [17, 24]. Therefore, changes in RE expression in the brain, including in the hippocampus (where neuronal stem cells are located) [31], can trigger AD development. The reasons for such changes in REs expression may be disease-associated polymorphic loci located in the REs regions [8-13], as well as aging, which causes the accumulation of tau and beta-amyloid [32]. In addition, during aging, activated REs cause inflammatory processes in the human body, including in the brain, due to interferon stimulation [33]. In experiments on SH-SY5Y cells, overexpression of various tau isoforms and their interaction with beta-amyloid led to locus-specific patterns of REs dysregulation (which indicates the involvement of strictly defined REs in the pathogenesis of the disease, rather than random or total changes), characteristic of AD [34]. Knockout of the same gene BMI1 (B cell-specific Moloney murine leukemia virus integration site 1) resulted in beta-amyloid deposition and tau protein accumulation in human postmitotic neurons [35], as well as derepression of REs [36]. This suggests a possible role for activated REs in the pathological accumulation and aggregation of beta-amyloid and tau. At the same time, amyloid aggregates cannot inhibit REs since deposits of pathological amyloid aggregates led to increased processing of noncoding RNAs from SINE B2 transcripts in the mouse hippocampus [37]. It can be hypothesized that antiviral tau inhibits REs similarly, whereas abnormal conformation and aggregation of tau protein renders it incapable of such inhibition. As a result, tauopathy leads to activation of ERVs, as has been shown in experiments on mice [38]. The role of tau in the epigenetic regulation of REs has been determined - tau-associated chromatin marks have been detected at HERV-Fc1 loci. The conducted RE profiling in

Drosophila throughout the brain has shown heterogeneous response profiles, including age- and genotype-dependent RE activation under the influence of tau [39]. A study of deceased human brains showed significant upregulation of LINE1, Alu [34], and LTR-RE [40] in AD patients compared to controls and heterochromatin decondensation with a substantial increase in HERV transcripts in AD [41].

Viral infections are also inducers of AD development. This is because beta-amyloid, associated with AD, is an immune system protein that protects against viral infections. Beta-amyloid accumulates in the brain in response to herpesvirus infection to protect against the virus. Beta-amyloid oligomers bind to the surface glycoproteins of the herpes virus, exerting an antiviral effect, but this accelerates the aggregation of beta-amyloid [42]. The antiviral capacity of beta-amyloid against influenza virus with modulation of virus interaction with phagocytes has been revealed [43]. HSV-1 (herpes simplex virus) infected hippocampal neurons show significantly greater beta-amyloid accumulation than uninfected ones [44]. In human microglial cells (3D spheroid models), an increase in the expression of beta-amyloid and tau (with an increased percentage of its phosphorylated forms) was determined under the influence of HHV-6 (human herpesvirus 6) [45]. Experiments on primary hippocampal neurons infected with HSV-1 revealed that tau protein is an acute response to any danger-associated molecular pattern (DAMP) [44]. In the brain of HIV-infected people, beta-amyloid aggregation is increased. The HIV (human immunodeficiency virus) transactivator of transcription (Tat) protein directly interacts with beta-amyloid, causing the formation of double-twisted fibrils with subsequent formation of thick unstructured strands and aggregates of homogeneous amyloid fibrils [46].

Herpesviruses, which are involved in the development of AD due to interaction with beta-amyloid [42, 44] and tau [45] with stimulation of its oligomerization and aggregation, are also activators of REs [47]. Influenza virus, targeted by the beta-amyloid antiviral response [43], also stimulates RE expression [48, 49]. The beta-amyloid aggregation-enhancing HIV [50] is characterized by an activating effect on REs [51]. The resulting activated REs are a component of AD progression (reflected by the activation of REs in the brains of AD patients [34, 40]) due to the interaction of these REs with the tau protein [39]. Since REs and viruses are evolutionarily related (REs evolved from viruses through germline insertions with intergenerational transmission) [52], the antiviral activity of beta-amyloid and tau may be reflected in their counteraction to REs activity. Indeed, a role has been discovered for these antiviral proteins in inhibiting REs, the expression products of which, in turn (like viruses), stimulate the expression of beta-amyloid and tau, interacting with them and causing their pathological conformation and aggregation [34-38]. As a result, a "vicious circle" contributes to AD's progression (Figure 1). Pathological changes in neurons in AD may be stimulated by genomic instability [4], which is caused by somatic recombinations between REs such as Alu and LINE1 [53], as evidenced by FISH analysis of individual brain neurons in patients with AD [54]. It is necessary to elucidate in more detail the effect of REs on AD development since a promising therapeutic impact that prevents pathological transpositions of these elements can form the basis of targeted therapy for the disease.

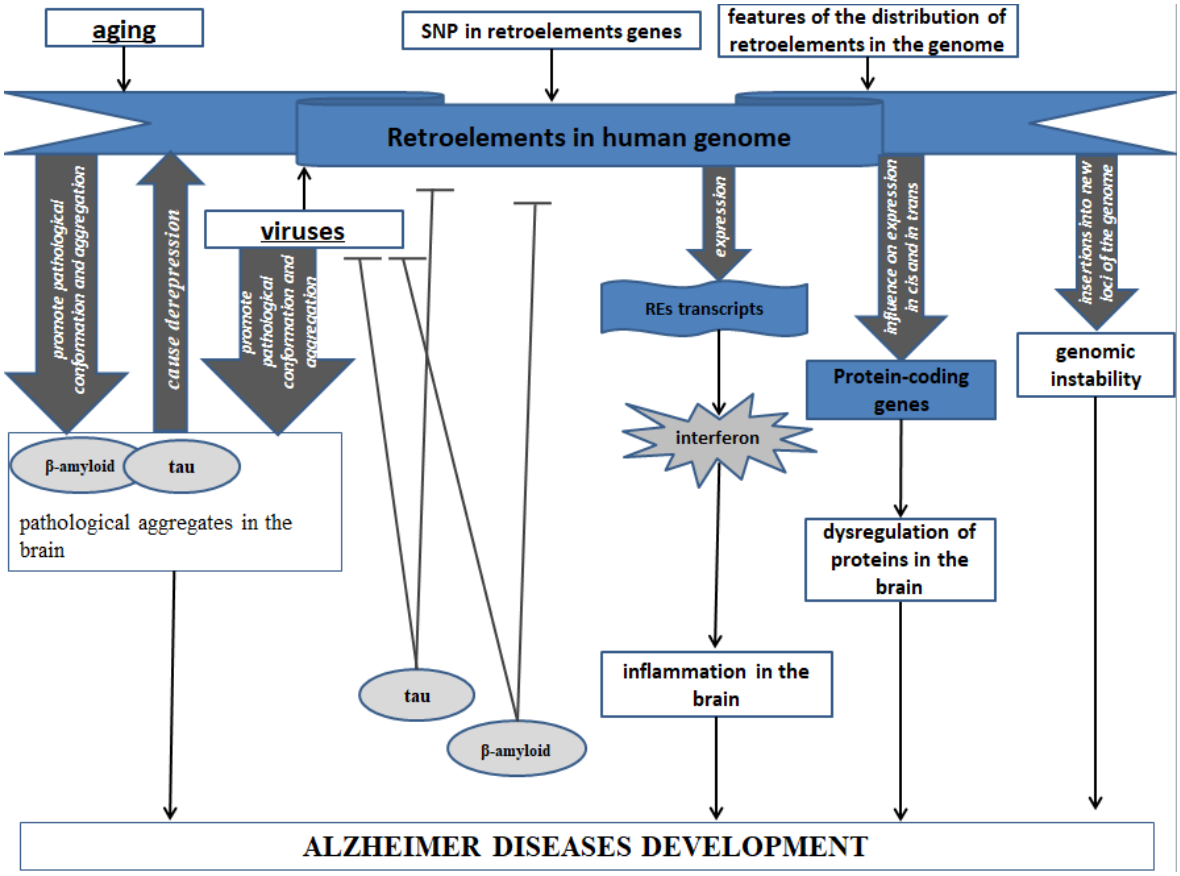

Figure 1 Scheme of retroelement involvement in AD pathogenesis via interactions with antiviral proteins tau and beta-amyloid (normal beta-amyloid and tau inhibit the activity of viruses and retroelements, but aggregates of these proteins formed during interaction with retroelements and viruses are not capable of such inhibition, resulting in derepression of retroelements).

2. Role of Retroelements in Alzheimer's Disease Development

Analysis of scientific literature allowed me to find many articles that indicate the involvement of REs in the development of AD. The G-quadruplex, derived from the evolutionarily conserved LINE1, was determined to suppress gene expression in AD neurons [55]. In patients with AD, the expression of BMI1, which suppresses the transcription of tau protein, is reduced in the brain [35]. At the same time, experiments on Bmi1+/- mice caused neurodegeneration due to the activation of REs [36]. At the same time, amyloid deposition in the hippocampus induces enhanced processing of noncoding RNAs from SINE B2 transcripts [37]. Transcriptomic analysis showed RE activation induced by aging and tau protein in the mouse brain. The most pronounced activation was determined for ERVs. In mice transgenic for tau protein expression, an increased number of DNA copies of REs was specified in the brain [38].

In blood samples of patients with AD, a higher methylation of LINE1 is detected compared to healthy people, indicating the possible role of these changes in disease pathogenesis [56]. However, in another study of blood samples from late-onset AD patients, a significant increase in the expression of 1790 transcripts of LINEs, LTRs, and SVAs was revealed before clinical phenoconversion (from average cognitive performance to AD manifestation), which the authors

called the retrotransposon storm [40]. HERV-K is detected significantly more frequently in the cerebrospinal fluid of patients with AD (56%) compared to healthy controls (8%) [57].

According to the analysis of postmortem brain tissue of patients with neurodegenerative tauopathies, it was found that decondensation of heterochromatin and a decrease in the levels of piRNA cause dysregulation of REs with a significant increase in the number of HERVs transcripts [41]. A more detailed study of the nature of such changes in the postmortem brain tissues of AD patients showed differential expression of several specific REs in association with neurofibrillary tau tangle loading. At the same time, global transcriptional activation was observed for HERVs and LINE1, and chromatin marks associated with tau proteins were found in the loci of the location of HERV-Fc1. Brain-wide profiling of REs in Drosophila expressing human wild-type and mutant tau showed heterogeneous response profiles, including age- and genotype-dependent activation of REs under the influence of tau proteins [58]. Recent studies of postmortem brain tissue from AD patients also confirmed the activation of LINE1s and Alus compared to controls [34]. In addition, the association of AD with aging [3] is evidence of the involvement of REs in disease pathogenesis since REs are critical factors in aging [59].

Additional evidence for the role of REs in AD development is the data on the involvement of ncRNA in this pathology since REs are evolutionary [60] and direct [61, 62] sources of lncRNAs. Therefore, the relationship of lncRNAs with AD is additional evidence of the effect of REs on this disease. LncRNAs (such as lncRNA2393) have been shown to control neurogenesis gene expression in the hippocampus [63]. Since neuronal stem cells are located in the dentate gyrus of the human hippocampus, where episodic and spatial memory is formed [63], the data obtained indirectly indicate the involvement of lncRNAs in neurodegeneration. In AD, a change in the expression of lncRNA XIST was determined, and an object for AD treatment was considered [64]. LncRNAs also influence AD development due to their regulatory effect on miRNAs. For example, lncRNA NEAT1 suppresses miRNA-27a-3p expression, thus contributing to AD progression [65]. MicroRNAs are the most promising tools and targets for AD treatment since they regulate the expression of protein-coding genes and REs [27], which dysregulation in AD is described above.

3. Relationship of Noncoding RNAs with Retroelements in Alzheimer's Disease

The regulatory effect of microRNAs on REs is due to their evolutionary relationship since RE genes are the sources of microRNA genes in all living organisms, including humans. In 2016, Wei et al. created MDTE DB, a database for microRNAs derived from Transposable elements [66]. This may explain that, like REs, many miRNAs are involved in the pathogenesis of AD. A systematic review of scientific literature showed significant change in the level of 44 different microRNAs in the blood, 153 microRNAs in the cerebrospinal fluid, and 250 microRNAs in the brain of AD patients [67]. A significantly higher number of expressed miRNAs in the brain is also consistent with increased RE activity [26], which is also dysregulated in AD [34, 39-41]. Therefore, the analysis of miRNAs presented in MDTE DB can show one of the mechanisms of AD pathogenesis upon activation of REs.

My analysis of the scientific literature made it possible to determine the association of specific REs-derived miRNAs associated with AD. Analysis of brain samples from deceased AD patients showed an increased level of miR-1202 [68] derived from LINE1 [66]. MiR-1246, which originated from ERVL of the endogenous retrovirus [66], was proposed as a biomarker of AD to determine its level in the blood serum of patients since their level of this microRNA is significantly increased [69].

Decreased levels of miR-1271 were found in the brains of deceased AD patients [70]. This miRNA was originated from LINE2 [66].

LINE2 is a source of miR-151a [66], which expression is increased in AD patients [71]. The search for potential biomarkers and therapeutic agents for AD, integration of transcriptomic data with protein-protein and transcriptional regulatory interactions showed the role of miR-192-5p (derived from LINE2 [66]) and miR-335-5p (derived from SINE/MIR) [66] as crucial signaling and regulatory molecules associated with transcriptional changes in AD. Levels of these miRNAs decrease in the blood of AD patients [72] and to miR-192-5p in the hippocampus of experimental mice [73]. Further studies have shown the potential protective efficacy of miR-192-5p in AD. The level of this microRNA decreased during exercise and contributed to a decrease in the expression of TNF-α, IL-6, and IL-1β involved in inflammatory reactions in AD [73]. Similar results were obtained in experiments on cell cultures and mice modeled for AD to miR-335-5p, which can be used for targeted therapy of the disease [74].

Experimental studies in mice have shown the role of miR-211 (derived from LINE2 [66]) in the pathogenesis of AD due to a direct effect on NUAK1, which reduced the survival of neurons with progressive accumulation of beta-amyloid [75]. Elevated miR-211 expression was detected in another AD model mouse study with beta-amyloid accumulation [76]. In 2017, an increased level of miR-28-3p (the miR-28 family comes from LINE2 [66]) in the cerebrospinal fluid was detected in AD model mouse [77]. In the blood serum of AD patients, the concentration of miR-28-3p was also increased compared to healthy controls. The level of this microRNA decreased with the practical results of donepizil therapy [78]. LINE2 was a source of miR-31 [47], which low expression was found in patients with AD [79]. Moreover, experiments in mice with modeled AD showed that lentivirus-mediated expression of miR-31 significantly improved neurological performance by dramatically reducing beta-amyloid accumulation in the hippocampus and its base [80].

A genome-wide linkage analysis determined a significant association of the miR-320 gene location locus in patients with late-onset familial AD [81]. Increased expression of miR-320 in brain neurons was determined in AD model mice [82]. ERVL is an evolutionary source of miR-3200 [66], the level of which is reduced in the blood of patients with AD [71]. In AD, reduced expression of miR-325 is determined (derived from LINE2 [66]). This microRNA has a post-transcriptional regulatory effect on the synthesis of tomosin (impairs synaptic transmission in the brain) in the hippocampus [22]. Low levels of miR-342-5p (derived from SINE [66]) have been identified in patients with worse AD [83]. SINE/MIR-derived miR-3646 was characterized by increased expression in AD patients [84]. Analysis of blood DNA samples from AD patients showed a significant increase (compared to control) in the level of miR-378a [85], which originated from SINE/MIR [66]. This miRNA was proposed as a biomarker for AD [85].

AD patients are characterized by overexpression of miR-384 (derived from LINE [66]), which interacts with mRNA of the BACE1 protein (beta-secretase catalyzing the conversion of amyloid precursor to beta-amyloid) [86]. Decreased level of miR-4286 [68] derived from ERVL [66] and miR-4422-5p [87] was determined in the blood serum of AD patients (derived from LTR/Gypsy [66]). A reduced level of miR-4487 (which originated from L1 [66]) was detected in brain neurons of AD patients [88]. The expression of miR-4504 (derived from L1 [66]) increases in the brains of AD patients [89]. LINE2 is an evolutionary source of miR-502 [66], which is reduced in the blood of AD patients [71]. Decreased expression of miR-511 (derived from LINE1 [66]) in AD promotes increased synthesis of the FKBP5 protein. The mRNA of this gene is a target for miR-511 [90]. Moreover,

treatment of AD model mice with cauterization at acupuncture points of the control vessel improved cognitive functions by restoring miR-511-3p expression [91].

In the blood plasma of AD patients, a decrease in the level of miR-545-3p compared to the control was determined [92]. miR-545 family evolved from LINE2 [66]. LINE1 is a source of miR-576-3p [66], which transcription is reduced in patients with AD [93]. A low level of miR-708-5p (derived from LINE2 [66]) was detected in blood samples of AD patients [94]. The data obtained were confirmed in the study of samples of nerve cells from AD patients [95]. SINE/MIR is a source of miR-885-5p [66], which expression is reduced in the blood of AD patients [96]. miR-885-5p overexpression attenuates beta-amyloid-induced cell damage by suppressing KREMEN1 synthesis [97]. Thus, the analysis of the scientific literature allowed me to identify 37 individual microRNAs derived from REs and involved in the development of AD. Of these miRNAs, 13 were found to be upregulated (Table 2), while 24 were downregulated in AD (Table 3). The different expression patterns of REs-derived microRNAs in AD can be explained by the fact that epigenetic regulation of gene expression in the brain has a complex, multidirectional nature [18]. The hyperactivated REs involved in these processes can inhibit and enhance their derived microRNAs' expression. The increased expression is due to the direct formation of microRNAs from RE transcripts (and not just their evolutionary origin) [98]. The downregulation of REs-derived miRNAs is due to binding to REs transcripts, which act as sponges for these miRNAs [99], similar to lncRNAs since processed LINE [62] and ERV [61] transcripts themselves can function as lncRNAs. Based on the analysis presented in Table 2 and Table 3, it can be assumed that the predominant effect of increased RE expression in AD is a decrease in REs-derived microRNAs.

Table 2 Retroelement-derived microRNAs that are overexpressed in Alzheimer's disease.

N	miRNA	retroelement, miRNA source	expression change	reference
1.	miR-1202	LINE1	increased	[68]
2.	miR-1246	ERVL	increased	[69]
3.	miR-151a	LINE2	increased	[71]
4.	miR-211	LINE2	increased	[75, 76]
5.	miR-28	LINE2	increased	[77, 78]
6.	miR-320	LINE1	increased	[82]
7.	miR-3646	SINE/MIR	increased	[84]
8.	miR-378a	SINE/MIR	increased	[65]
9.	miR-384	LINE/Dong-R4	increased	[86]
10.	miR-4504	LINE1	increased	[89]
11.	miR-495	ERVL	increased	[100]
12.	miR-517	SINE/Alu	increased	[101]
13.	miR-566	SINE/Alu	increased	[102]

Table 3 Retroelement-derived microRNAs that are downregulated in Alzheimer's disease.

N	miRNA	retroelement, miRNA source	expression change	reference
1.	miR-1271	LINE2	decreased	[70]
2.	miR-192	LINE2	decreased	[72, 73]
3.	miR-31	LINE2	decreased	[79, 80]
4.	miR-3199	LINE2	decreased	[103]
5.	miR-3200	ERVL	decreased	[71]
6.	miR-325	LINE2	decreased	[22]
7.	miR-335	SINE/MIR	decreased	[72, 74]
8.	miR-342	SINE	decreased	[83]
9.	miR-4286	ERVL	decreased	[68]
10.	miR-4422	LTR-Gypsy	decreased	[87]
11.	miR-4487	LINE1	decreased	[88]
12.	miR-4772-3p	LINE1	decreased	[104]
13.	miR-502	LINE2	decreased	[71]
14.	miR-511	LINE1	decreased	[90, 101]
15.	miR-545	LINE2	decreased	[92]
16.	miR-576	LINE1	decreased	[93, 105]
17.	miR-582	LINE/CR1	decreased	[89]
18.	miR-659	LINE2	decreased	[104]
19.	miR-6087	LINE1	decreased	[106]
20.	miR-619	LINE1	decreased	[107]
21.	miR-659	LINE2	decreased	[104]
22.	miR-664	LINE1	decreased	[108]
23.	miR-708	LINE2	decreased	[94, 95]
24.	miR-885	SINE/MIR	decreased	[96, 97]

Since AD is associated with aging [3], it makes sense to analyze the scientific literature on the involvement of 37 described miRNAs in aging. The obtained result could be an additional confirmation of the assumption about the role of REs in AD development because REs are involved in the mechanisms of aging since the pathological activation of REs due to various mechanisms [59], including loss of SIRT6 labels [109], is a factor in aging [27], and in neurodegenerative diseases, genomic instability is noted with activation of REs in neurons [39]. It is likely that the changes in the activity of REs that occur during aging contribute to changes in the expression of microRNAs, which, if expressed pathologically, are triggers for AD development. Since all AD patients have a common pathogenesis with the accumulation of beta-amyloid and tau proteins, there should be common mechanisms of pathological activation of REs during aging, resulting in an imbalance in epigenetic regulation in the form of changes in miRNA expression. Therefore, I searched the scientific literature for microRNAs derived from REs, the expression of which changes both in AD and aging. As a result, 12 such microRNAs were identified (Table 4 and Table 5), indicating that specific REs' activation triggers aging and associated degeneration in the brain and AD triggers. MicroRNAs derived from

REs that were discovered are promising as tools for epigenetic therapy and possible diagnostic markers of AD. As shown in Table 4 and Table 5, in AD 4 REs-derived miRNAs (miR-192, -211, -378a, -511) showed similar expression changes with aging, which may indicate the role of aging mechanisms with dysregulated REs as triggers for AD development. However, Table 5 shows 8 REs-derived miRNAs which expression is altered in opposite directions in aging and AD. This suggests that AD is triggered by aging and individual differences in REs activation, some of which are AD-associated polymorphisms located in the REs localization regions of the human genome [8-13].

Table 4 Similar changes in expression of retroelement-derived microRNAs in aging and Alzheimer's disease.

N	miRNA (RE-source)	changes in miRNA levels in Alzheimer's disease (References)	changes in miRNA levels during aging (References)
1.	miR-192 (LINE2)	decreased ([72, 73])	decreased ([110])
2.	miR-211 (LINE2)	increased ([75, 76])	increased ([111])
3.	miR-378a (SINE/MIR)	increased ([65])	increased ([58])
4.	miR-511(LINE1)	decreased ([90, 91])	decreased ([90])

Table 5 Opposite changes in expression of retroelement-derived microRNAs in aging and Alzheimer's disease.

N	miRNA (RE-source)	changes in miRNA levels in Alzheimer's disease (References)	changes in miRNA levels during aging (References)	Genes which mRNAs are targets of these microRNAs
1.	miR-151a (LINE2)	increased ([71])	decreased ([112])	*FAM120AOS, AGO, RPS6KA5, ME1, COL25A1, UPP2*
2.	miR-28 (LINE2)	increased ([77, 78])	decreased ([113])	*FOXO1*
3.	miR-31 (LINE2)	decreased ([79, 80])	increased ([114, 115])	*ZMYM5, CHMP4B, ELOC, RXFP1, HAUS4, PRSS23, MASP1*
4.	miR-320c (LINE2)	increased ([82])	decreased ([116])	*YOD1, CDKL5, ONECUT2, SPOPL, SH2B3, PLPPR1, KITLG, GPBP1, GCG*
5.	miR-335 (SINE/MIR)	decreased ([72, 74])	increased ([117])	*ZBTB10, RAD23B, LRP2, TMEM56, SLC36A4, GUCY1A2, TOX3, SCN3B, PDIK1L, ATRNL1, PLCB4, ZMYM4, TEAD1*
6.	miR-576 (LINE1)	decreased ([93, 105])	increased ([118])	*GLUL1, FGL2, VWA3B, RORA, ADGRB3, NDUFAF5*
7.	miR-708 (LINE2)	decreased ([94, 95])	increased ([119])	*Akt1, CCND1, MMP2, EZH2, Parp-1, Bcl2*
8.	miR-885 (SINE/MIR)	decreased ([96, 97])	increased ([120])	

An analysis of the literature data on downstream targets for microRNAs that have opposite changes in expression during aging and AD was conducted. As a result, it was found that the expression of miR-151a (the level of which is increased in AD and decreased in aging) is associated with ischemic stroke, which indicates its involvement in pathological rather than physiological (aging) processes in the brain [121]. According to the miRDB database (https://miRdb.org), miR-151a targets mRNAs of the *FAM120AOS, AGO, RPS6KA5, ME1, COL25A1, UPP2* genes. MiR-28 is also involved in the pathological process, contributing to glioblastoma development. This microRNA reduces the expression of *FOXO1* [122]. Elevated levels of miR-320c have been identified in traumatic brain injury, indicating the involvement of this microRNA in pathological processes [123, 124]. The targets of miR-320c are mRNAs of the genes *YOD1, CDKL5, ONECUT2, SPOPL, SH2B3, PLPPR1, KITLG, GPBP1, GCG*. For 5 other microRNAs (miR-31, miR-335, miR-576, miR-708, miR-885), increased expression was determined in physiological aging and low expression in AD. MiR-31 has antitumor properties, i.e., it is aimed at normalizing brain processes by inhibiting radixin expression [125]. The targets of this microRNA (https://miRdb.org) are mRNAs of the *ZMYM5, CHMP4B, ELOC, RXFP1, HAUS4, PRSS23, MASP1* genes. MiR-335 prevents cell apoptosis by affecting the expression of ROCK2 [126]. MiR-335 also targets many other genes, such as *ZBTB10, RAD23B, LRP2, TMEM56, SLC36A4, GUCY1A2, TOX3, SCN3B, PDIK1L, ATRNL1, PLCB4, ZMYM4, TEAD1* (https://miRdb.org). Mir-576 inhibits the migration and proangiogenic properties of glioma cells by inhibiting hypoxia-inducible factor-1α (HIF-1α) and induces a reduction in the protein levels of matrix metalloproteinase-2 and vascular endothelial growth factor [127]. MiR-576 also targets mRNAs of the *GLUL1, FGL2, VWA3B, RORA, ADGRB3, NDUFAF5* genes. MiR-708 acts as a tumor suppressor in human glioblastoma cells, reducing the expression of *Akt1, CCND1, MMP2, EZH2, Parp-1, and Bcl2* [128]. MiR-885 Inhibits Angiogenesis and Growth of Non-Small Cell Lung Cancer Brain Metastases [129]. Thus, the analysis of the functioning of REs-derived miRNAs showed that those that increase expression in AD and decrease expression in physiological aging exhibit oncogenic properties and contribute to pathological processes in the brain due to the effect on mRNA of specific target genes. At the same time, microRNAs whose levels are reduced in AD and increased in physiological aging, on the contrary, exhibit antitumor properties, acting as tumor suppressors, i.e., are aimed at normalizing physiological processes.

As can be seen from Table 4 and Table 5, out of 12 microRNAs derived from REs common to aging and AD that I identified, 9 originated from autonomous LINEs, 3 – from SINEs, which may indicate a predominant dysregulation of strictly defined REs in AD, due to common mechanisms with aging. It is most likely that the evolutionarily programmed species-specific expression of certain LINEs in individual brain cells fails during neurogenesis in aging. As a result, unprogrammed activation of LINEs occurs, which can sometimes serve as a trigger for AD development. Indeed, various studies have shown that mosaicism in LINE retrotranspositions serves as the basis for epigenetic programming of individual neurons in the brain not only in humans [130] (especially in neuronal stem cells of the hippocampus [26]) but also in mice [131] and Drosophila [132], which confirms my assumption. Experiments on these animals have shown the role of pathological changes characteristic of AD in the activation of REs. For example, in mice, pathological tau conformations lead to the activation of ERVs (which may be associated with derepression of these REs, since tau normally inhibits retroelements) [38]. In the Drosophila brain, tau-associated chromatin marks have been identified at ERV sites, further suggesting that tau exerts a controlling effect on REs expression

at the genomic level [39]. In humans, tauopathy also leads to increased expression of HERV [40, 41], LINE1, and Alu [34] in the brain.

The data obtained can become the basis for targeted therapy for AD aimed at normalizing the expression of REs using miRNAs. This direction may be due to the complete complementarity of nucleotides derived from REs microRNAs, which can be used as guides in the mechanisms of RNA-directed DNA methylation [133]. Additional treatment options may include epigenetic factors that remodel chromatin, methotrexate [134], and remodelin (an inhibitor of the enzyme N-acetyltransferase 10) [135]. Antibodies against HERV-K Env have also been proposed to eliminate its neurotoxicity [136], and antiviral drugs that inhibit prion-like protein propagation by targeting HERV proteins [137] have been proposed for the treatment of ALS, in the pathogenesis of which tau pathology [138] and retroelements associated with antiviral proteins also play a role [137]. Since SINE/MIR retroelements, which, according to Table 4 and Table 5 gave rise to 3 miRNAs common to aging and Alzheimer's disease, were derived from tRNAs [139], the scientific literature on possible links between tRNAs and ERs in Alzheimer's disease was reviewed to identify promising tools for the diagnosis and treatment of Alzheimer's disease.

4. Relationship of Transfer RNAs with Retroelements in Alzheimer's Disease

Mature tRNAs, in addition to transporting amino acids, have additional functions. They affect Alu polyadenylation [140], regulate pre-mRNA splicing by starting codon pairing [141], and function as insulators (forming functional complex for chromatin loops formation to regulate gene expression) [142]. The multifunctionality of tRNAs and the possible role of REs in the origin and evolution of their genes is evidenced by the large number of nuclear tRNA genes in eukaryotes, in contrast to bacteria and mitochondria (which evolved from bacteria). Specifically, the human genome has more than 610 tRNA genes in the nucleus of each cell, according to the human genomic tRNA database (gtRNAdb, hg19) [143]. Preserving such tRNA gene diversity in evolution is most likely due to the role of REs in their expansion, their involvement in epigenetic regulation of genome functioning, and their direct role in translation. Indeed, the distribution of tRNA genes in the human genome is characterized by forming 277 clusters [144]. Multifunctionality of tRNAs is also evidenced by studies of SINE2 (originated from tRNAs in evolution), which act as insulators [145], promoter sources (25% of all human promoters contain RE sequences, most of which originate from SINE) [146], regulators of reverse splicing for circular RNAs formation [147], tissue-specific gene enhancers [148]. SINE2 is also a source of brain-specific lncRNAs (and other tissue-specific lncRNAs) [149].

tRNAs are closely related to all epigenetic factors, both as their targets and tools for regulation. For example, mature tRNAs undergo pseudouridylation, which is necessary to perform specific functions [20]. Like REs, they are sources of noncoding RNAs (tsRNAs – tRNA-derived small RNAs). tRNAs themselves are actively involved in epigenetic regulation since tRNAs are processed into 4 types of fragments (tRFs): 3'-terminal tRF-3, 5'-terminal tRF-5, tRF-1 (3'-tRNA precursor fragment) [19, 150] and internal tRF (tRF-2 - arises from the anticodon loop) [151]. In humans, tRF-3s and tRF-5s interact with AGO proteins and function like miRNAs to cause silencing of target mRNAs. The formation of tsRNAs occurs specifically depending on tissue and stage of development. They are evolutionarily more conservative than miRNAs and present in the same abundance in cells [150]. Mature tRNAs are cleaved into functional tRNA halves, particularly inhibiting translation initiation due to interaction with ribosomes during stress [152]. The formation of tRNA halves is not the

product of random degradation of tRNA but is catalyzed by a specific enzyme, Angiogenin (ANG) endonuclease [153].

Various animal experiments have identified mRNAs' role in AD development. It has been shown that inactivation of CLP1 RNA kinase, which is involved in tRNA splicing, causes neurodegeneration in mice with tRF accumulation [154]. Comparative analysis of tsRNAs expression showed a significant difference in the expression of 27 tsRNAs (upregulated 14 and down-regulated 13) in APP/PS1 transgenic mice (AD model) compared to wild-type control mice. Target mRNAs of all differentially expressed tsRNAs are involved in learning and memory, the metabolic process of amyloid-beta, and synaptic transmission [155]. In mice modeled for neurodegenerative disorders with accelerated aging (SAMP8), differential expression of 8 out of 570 tRFs was detected compared to control (SAMP1). The target genes of these 8 tRFs are 110 miRNA genes involved in synapse formation and synaptic vesicular cycle pathways [156]. Another study found significant dysregulation of 13 out of 387 expressed tsRNAs in the hippocampus of AD model rats compared to controls. Expression change of 57 tsRNAs was also noted when exposed to the traditional Chinese medicine prescription (Bushen Tiansui formula) for the treatment of AD, which indicates the role of tsRNAs as disease biomarkers and determining the effectiveness of disease treatment [157].

Since the hippocampus is characterized by a pronounced activation of REs in neuronal stem cells, which is associated with their epigenetic programming for further zone-specific differentiation [26], it can be assumed that the observed changes in tsRNAS expression are due to the influence of REs, which is associated with their close evolutionary relationship and the presence of common properties. Indeed, like RE transcripts, which can form different functional molecules depending on the systems that process them (microRNAs using RISC [27], lncRNAs, and mature mRNAs translated into proteins using the spliceosome [61, 62]), tRNAs form mature tRNAs necessary for the transfer of amino acids with the help of a spliceosome, are processed into tRFs with the help of the RISC system [150], and with the help of ANG - into tRNA halves [153].

The use of tRNAs as primers for the reverse transcription of LTR-REs indicates the evolutionary relationship of tRNAs with REs [158, 159]. At the same time, tRNA-derived tRFs within the RNAi system inhibit REs reverse transcription by binding to a highly conserved tRNA primer binding site [29]. In the human genome, tRF-3s are highly complementary to LTR-REs [160]. This is similar to the relationship between REs and miRNAs, since miRNAs formed in evolution from REs are also characterized by REs silencing due to the presence of complementary sequences [17]. In addition, tRNAs in eukaryotic genomes are used as the basis for the formation of common non-autonomous REs (SINE2) [139].

A joint property of REs (SINEs) and tRNAs is that they are transcribed by RNA polymerase III [161]. In addition, it turned out that some previously annotated miRNAs were tRFs (miR-4454 [162], miR-1260a, miR-1260b, miR-3182, miR-4521, miR-7977 microRNAs are tRF molecules [163]), which also indicates the evolutionary origin of tRNAs from REs and their close relationship because REs are important evolutionary sources of miRNA genes [66]. In addition, this can function as oncogenes [164, 165], tRNA halves promote cell proliferation [166], while REs and microRNAs derived from them also stimulate carcinogenesis [27].

Experiments on mice [167] and rats [168] modeled for Alzheimer's disease on the effects of intermittent fasting and accumulation of beta-amyloid showed an improvement in the condition and a decrease in the accumulation of beta-amyloid. The data obtained can be compared with experiments on the effect of starvation on the increase in life expectancy and suppression of

carcinogenesis [169], in which RE activation plays an important role [27]. It can be assumed that activated REs contribute to the accumulation of amyloid with age indirectly due to the influence of ncRNAs formed from their transcripts and to the stimulation of miRNAs and mRNAs by retroelements.

Human studies have also shown a role of tsRNAs in AD development. Since women with Alzheimer's disease develop more accelerated dementia and loss of cholinergic neurons compared to men, changes in the transfer of tRFs to cholinergic transcripts in brain regions enriched in cholinergic neurons were investigated. RNA sequencing of single cells in the temporal cortex showed lower levels of tRFs in women with AD, which correlated with increased levels of cholinergically-associated mRNA targets [2]. A reduced level of ANG is determined in the blood serum of AD patients, which correlates with impaired cognitive functions. This explains the pathological angiogenesis and inflammation in AD along with the role of vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), and tumor necrosis factor α (TNF-α) [170]. Since ANG is used for tRNA halves formation [153], the association of heterozygous nonsense mutations in the ANG gene with the disease in patients with familial cases of AD indicates the role of tRNA halves in the pathogenesis of AD [171]. In the study of hippocampal samples from deceased people using qRT-PCR and western blot, there was a significant change in the expression of tRFs in AD and increased expression of ANG compared with the brains of people without AD. In AD patients younger than 65 years of age, a decrease in the levels of NSun2 (RNA methyltransferase 2), which modifies tRNA through methylation and enhances tRF production, was found [172].

5. Conclusion

AD is a multifactorial disease in which genetic factors play an essential role. Of the many genes whose allelic variants are associated with AD (*PSEN1, PSEN2, APP, ABCA7, BIN1, PICALM, TREM2, CR1, APOJ, MTHFR, BIN1, APH1B, BIN1, CASS4, CCDC6, NCK2, PILRA, PTK2B, SPRED2, TSPAN14*), the involvement in the pathogenesis of AD can most reliably be explained for the *PSEN1, PSEN2*, and *APP* genes. Alzheimer's disease-associated polymorphisms are located mainly in intronic and intergenic regions where retroelement genes and ncRNAs derived from them are located. Therefore, these associations indicate a role for retroelements in the pathogenesis of Alzheimer's disease. Moreover, the role of viruses causing beta-amyloid and tau protein pathology in retroelement activation has been described. Since retroelements evolved from integrated viruses, beta-amyloid and tau normally function as a defense against retroelement activity in the brain. However, with aging, under the influence of viral infections and individual polymorphisms in the regions of retroelement location, REs are pathologically activated and cause proteinopathy and aggregation of beta-amyloid and tau. Since the expression of these antiviral proteins is enhanced by retroelement transcripts, a "vicious circle" is formed (Figure 2) since elevated concentrations of beta-amyloid and tau aggregate under the influence of retroelements, and the resulting aggregates are unable to inhibit retroelements, causing their derepression. As a result, brain pathology in Alzheimer's disease progresses. Indeed, REs are drivers of the epigenetic regulation of neurons, programming their differentiation. Pathological activation of REs is a factor of aging, including the brain age-related degeneration. Analysis of scientific literature allowed me to find studies confirming the role of REs in AD development. Indirectly, I established the role of REs in AD development by analyzing MDTE DB – 37 microRNAs derived from REs were identified, the

expression of which changes explicitly in AD. Moreover, further analysis of the scientific literature allowed me to find that 12 of these 37 miRNAs are also associated with aging. This allows me to hypothesize about the role of REs involved in aging in AD pathogenesis. I suggest that REs hyperactivation in aging is a trigger for AD development, one of the results of which is the deposition of beta-amyloid and tau proteins. Since 3 microRNAs associated with aging and AD originated from SINE/MIR, which evolved from tRNAs, I analyzed the relationship between tRNAs and REs in AD. As a result, I described the evolutionary and functional relationships between REs and tRNAs and the role of tRNAs in AD development. The data obtained can become the basis for targeted therapy for AD aimed at normalizing the expression of REs using miRNAs. This direction may be due to the complete complementarity of nucleotides derived from REs microRNA, due to which such microRNAs can be used as guides in the mechanisms of RNA-directed DNA methylation. Additional therapy factors may include epigenetic factors that remodel chromatin – methotrexate and remodelin (an inhibitor of the enzyme N-acetyltransferase 10). Antibodies against HERV-K Env have also been proposed to eliminate its neurotoxicity, and antiviral drugs that inhibit prion-like protein propagation by targeting HERV proteins have been proposed for the treatment of ALS, in the pathogenesis of which tau pathology and retroelements associated with antiviral proteins also play a role.

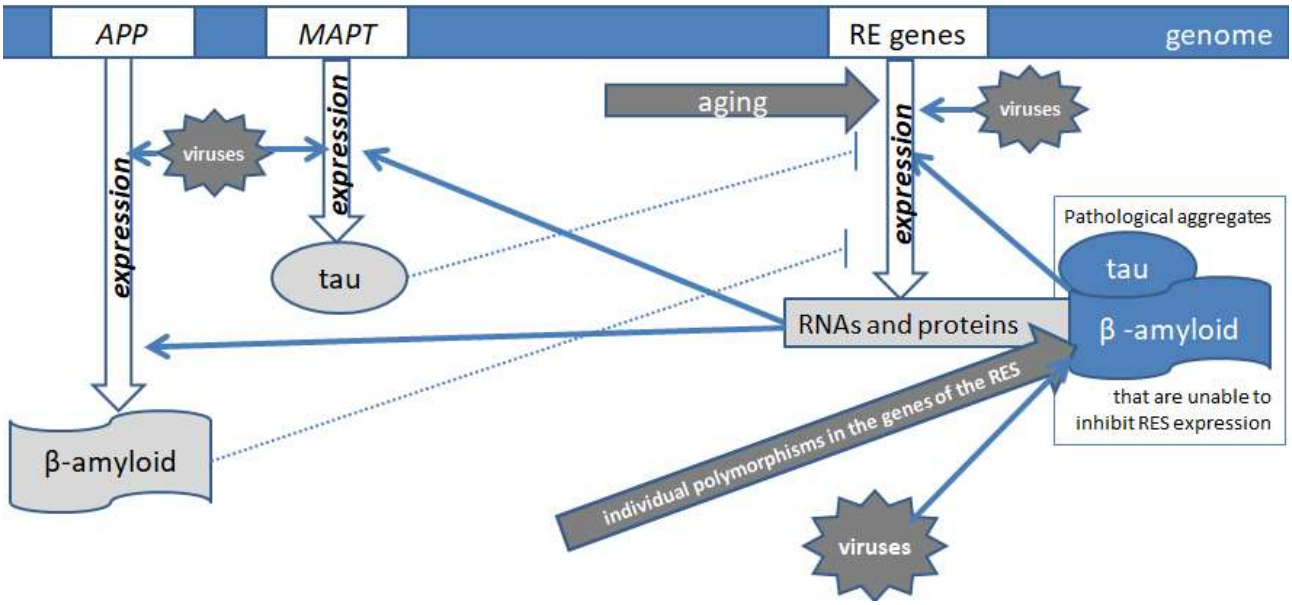

Figure 2 Scheme of "vicious circle" formation in the pathogenesis of Alzheimer's disease (Normal proteins tau and beta-amyloid inhibit expression of retroelements. However, the formation of pathological aggregates during the interaction of retroelements (under the influence of polymorphisms, aging, and viruses) causes derepression of retroelements. This, in turn, further enhances the expression of beta-amyloid and tau, which again interact with retroelements, forming new aggregates).

Abbreviations

AD	Alzheimer's disease
ERV	endogenous retrovirus
LINE	long interspersed nuclear element
lncRNA	long noncoding RNA
LTR	long terminal repeat
ncRNA	noncoding RNA
REs	retroelements
RNAi	RNA interference
SINE	short interspersed nuclear element
SVA	SINE-VNTR-Alu retroelement
TEs	transposable elements
tRNA	transfer RNA
tsRNA	tRNA-derived small RNA

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