NARRATIVE REVIEW

Non-coding RNAs and their role in Alzheimer's pathogenesis

Ali Maavaeian [1], Hossein Mohebi [1], Kawsar Ahmed [2,3,*]

[1] Department of Orthopedic Surgeon, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Department of Information and Communication Technology, Group of Bio-photomatix, Mawlana Bhashani Science and Technology University, Santosh, Tangail, Bangladesh

[3] Department of Electrical and Computer Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, Canada

Highlights

• Alzheimer's disease is a progressive and irreversible brain impairment in the elderly.
• Beta-amyloid plaques and neurofibrillary tangles are the main pathological symptoms of Alzheimer's.
• Non-coding RNAs could involve in the pathogenesis of Alzheimer's disease.

Graphical Abstract
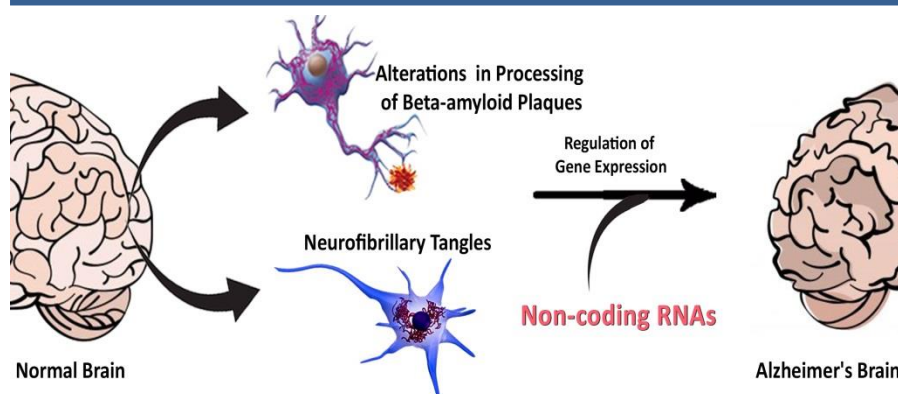
Abstract

Alzheimer's disease is a progressive and irreversible brain disorder. This disease is the most common reason for dementia in aged people. Pathological symptoms of this disease are the formation of beta-amyloid plaques and neurofibrillary tangles. Beta-amyloid plaques appear intercellularly, while neurofibrillary tangles appear intracellularly. Defects in genes such as PSEN, APP, BACE1, etc., can cause Alzheimer's. However, some mechanisms that alter gene expression can have the main role in disease pathogenesis. One of the post-transcriptional mechanisms that can alter gene expression is the involvement of non-coding RNAs. Many kinds of non-coding RNAs exist, two of which are microRNAs and long non-coding RNAs. These can alter the expression of many genes by influencing the stability or structure of mRNAs. Non-coding RNAs can alter the risk of Alzheimer's disease if they affect genes involved in Alzheimer's pathogenesis. The mechanisms of influence of non-coding RNAs on the onset and development of Alzheimer's are not clear. This study aimed to describe the mechanisms of involvement of non-coding RNAs in the pathogenesis of Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a progressive neurological disorder that can affect the central nervous system and cause dementia, especially in the elderly. The main pathological properties of this illness are the formation of neurofibrillary tangles (NFTs) and amyloid-beta plaques (1). Neurofibrillary tangles form inside the cell and appear as accumulated and hyperphosphorylated forms of tau protein. But amyloid-beta (Aβ) plaques could aggregate intracellularly, and families with mutations in the Aβ-processing genes experience premature Alzheimer's accumulation (2). Although the formation of NFTs and Aβs are hallmarks of Alzheimer's, it is a multifactorial illness that impacts multiple cell signaling cascades. Among the pathways involved in this disease are apoptosis, synaptic dysfunction, excessive calcium influx, oxidative stress, neuroinflammation, and mitochondrial dysfunction. In addition, Aβ interacts with non-neuronal cells. For example, in the initial phases of Alzheimer's, Aβs are cleared by microglia, but later in the disease, these same cells release proinflammatory cytokines and exacerbate the symptoms of the disease (3, 4).

Mutations in the APOE, APP, Prsilinin-1 and Persilinin-2 genes and some other key genes could be one of the reasons for Alzheimer's disease, where changes are made to proteins. But changes in gene expression can also contribute to Alzheimer's pathogenesis. One of the mechanisms that cause gene silencing at the mRNA level is the involvement of non-coding RNAs (ncRNAs). These RNAs can be biologically active and perform their functions in the cell in different ways. These RNAs include microRNAs or miRNAs, Piwi-interacting RNAs or piRNAs, small interfering RNAs or siRNAs, and long non-coding RNAs or lncRNA (5, 6). MicroRNAs are a group of ncRNAs that play a vital role in regulating gene expression. Most microRNAs are first transcribed from the genome and then converted to mature MicroRNA by various enzymes such as Dicer and Drosha. They can interact with the downstream end of mRNA and prevent or even degrade their expression (7). Recently, miRNAs have been shown to be involved in many cellular pathways. These molecules have a vast expression in neurons in the brain tissue and contribute to synaptogenesis and differentiation of nerve cells. Further research has shown that changes in the profile of miRNAs in neurons can interfere with the pathogenesis of Alzheimer's disease (8, 9).

The other group of non-coding RNAs is lncRNAs, which produce longer transcripts of miRNAs and are similar in their maturation steps to their coding steps, which are performed in the nuclear space and then transferred to the cytoplasm. But they are not as protected as the coding genes. Studies have shown that the mammalian genome contains many lncRNAs loci that are not easy to classify. These molecules contribute to the cellular procedure, including cell proliferation, apoptosis, and pathological processes such as cardiovascular disease and nerve damage by affecting gene expression (10). lncRNAs may also be involved in Alzheimer's disease pathogenesis. An excellent example of this is a lncRNA called BACE1-AS, which is transcribed from the complement strand of beta-secretase-1 and directly interferes with the regulation of beta-secretase gene expression, causing the aggregation of Aβ in Alzheimer's (11). However, the exact role of ncRNA in the onset and progress of Alzheimer's is not well clear and further research is needed. This review aimed to describe the role of ncRNA in the pathogenesis of Alzheimer's disease.

Pathophysiology of Alzheimer's disease

In 1907, Alois Alzheimer was confronted by a 51 years female person with quickly declining memory as well as mental disorders, who died four years later. The most distinctive and common lesions in the brain of a patient with Alzheimer's are senile plaques (SP) and neurofibrillary tangles (NFT) (Figure 1) (12). NFTs are an important pathological symptom in the neuronal tissues of Alzheimer's disease. Neurons containing NFTs are characterized by dysfunction of the cytoskeleton and loss of microtubules and microtubule-associated proteins. Molecular mechanisms of cytoskeletal degradation and NFT development are relatively unclear. However, the processes of phosphorylation and dephosphorylation of proteins may contribute to the pathogenesis of this disorder. For example, tau peptide, a microtubule-associated protein, is highly hyperphosphorylated in the brains of Alzheimer's patients (13). Senile plaques are considered a pathological property of Alzheimer's disease

brain. These plaques are made of amyloid fibers composed of peptides of amyloid-beta (Aβ). These peptides are formed by the amyloid precursor protein (APP) cleavage. Genetic, in vitro, and in vivo observations show that the deposition of the peptides of Aβ in the brain is a key factor in Alzheimer's pathogenesis (14). Amyloid-beta peptides accumulate to soluble oligomers that act as activators of NMDAR endocytosis, neuroinflammation, incomplete neurogenesis, apoptosis, neuronal stress, synaptic dysfunction, lipid dysregulation, calcium over influx, oxidative damage, and mitochondrial dysfunction (15).
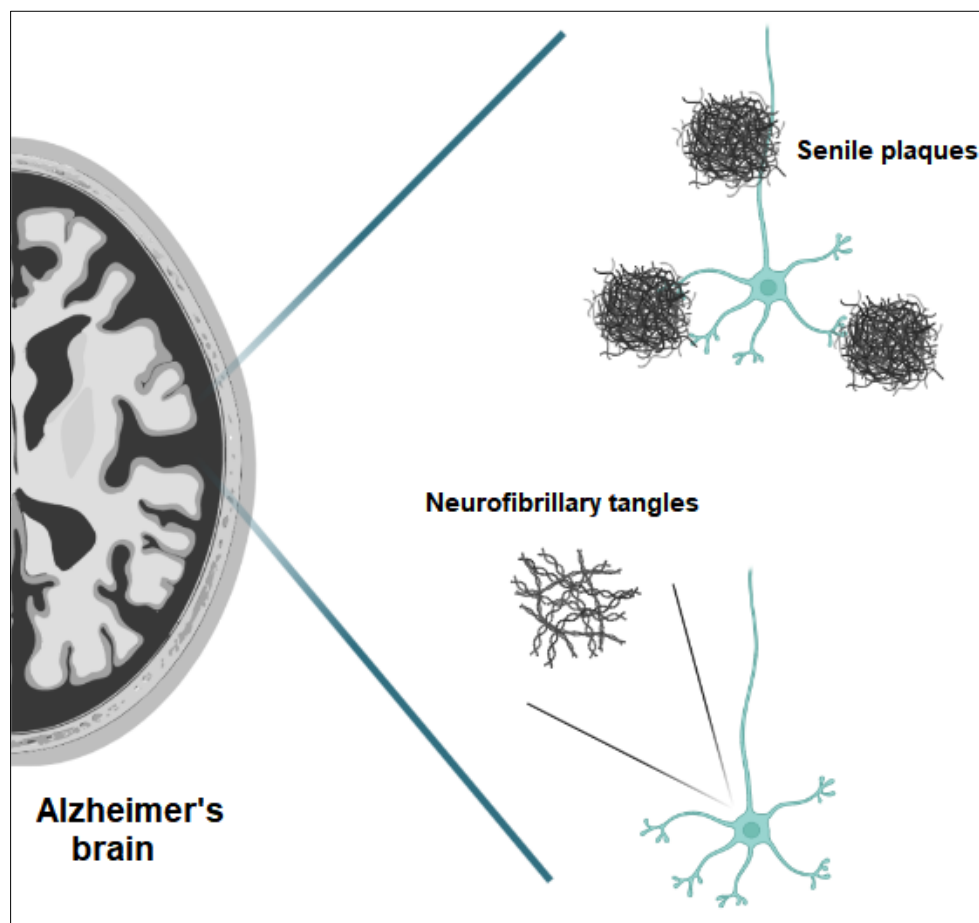

Figure 1. The main pathological properties of Alzheimer's disease. The two main features of Alzheimer's brain are the formation of beta-amyloid plaques and neurofibrillary tangles.

Small non-coding RNAs

There are different types of small non-coding RNAs (sncRNAs) that play many roles in the cell. Some are present in the spliceosome and some can contribute to the regulation of gene expression. Those sncRNAs involved in regulating gene expression can have a task in the progression of disorders, including neurodegenerative diseases. Among these, miRNAs have been further studied and identified, which can be considered biomarkers or tools for developing treatment strategies for these diseases (16). Major regulatory sncRNAs include miRNAs, siRNAs, and piRNAs, some of which are briefly described below.

MiRNAs are created by the regulation of the gene expression within a cell. They are about 21 to 23 nucleotides in size, transcribed through RNA Pol II, and are initially in the single-stranded RNA forms (pri-miRNAs). This structure is then processed by the Drosha/DGCR8 complex in the nuclear space to form the pre-miRNA hairpin structure. The last structure is transferred from the nuclear space to the cytosol by exportin-5 in an active transport way. Dicer, an RNase III, processes pre-miRNA into a mature double-stranded form in the cytoplasm. Mature miRNA is then detected, especially as a single strand, by the RISC complex. This complex directs miRNA to the target RNA and inhibits its expression or degrades it (Figure 2) (7).
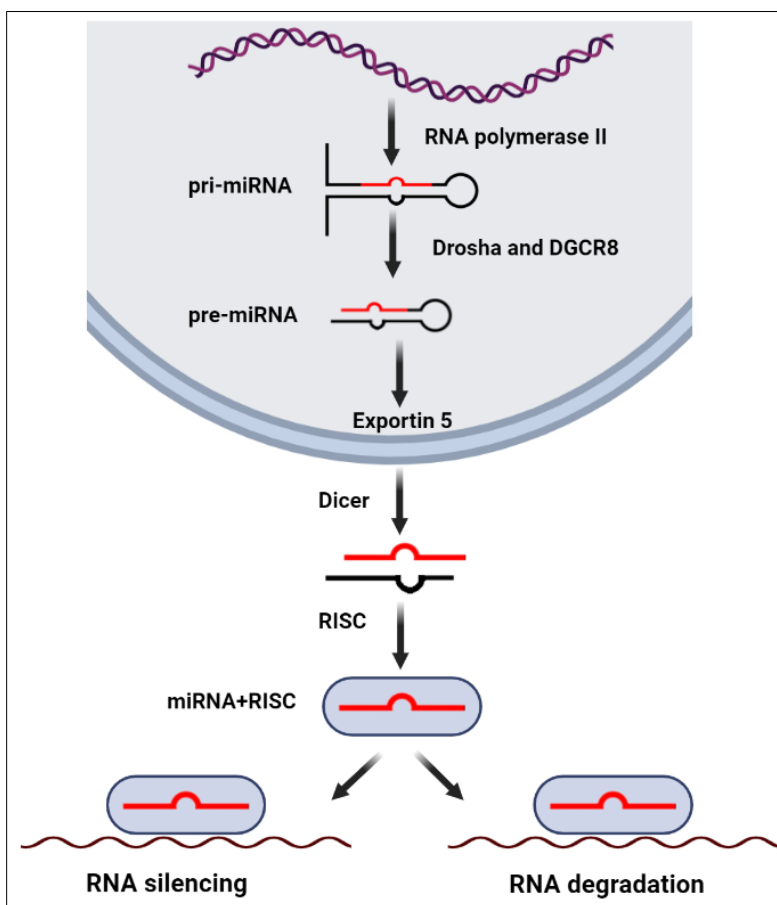
Figure 2. miRNA processing and performance steps. After the pri-miRNA transcription by RNA Pol II, it is processed to pre-miRNA in the nucleus by the Drosha and DGCR8 complex. Then pre-miRNA is transported to the cytosol by Exportin 5 and then becomes mature miRNA by Dicer. Mature miRNAs and the RISC complex degrade or inhibit target mRNA expression.

A specific miRNA in combination with the RISC complex can control the expression of many mRNAs. A large number of different microRNAs could also control a specific mRNA. These molecules are vastly present in the central nervous system and their presence varies at different times and in various regions of the brain (17). Examination of miRNA expression patterns in adult mice brains showed a specific set of miRNAs in the hippocampus and cerebral cortex (18). A closer look also showed that different patterns of miRNAs exist in various kinds of neurons and even various parts of the cell. For example, miRNAs such as miR-137-5p, miR-7-5p, miR-29a-3p, miR-318-3p, miR-322-5p, miR-339-5p and miR-200c-3p were observed in synapses (19). In the distal axons, miRNAs such as miR-221-3p, miR-204-5p and miR-16-5p were found (20). The specific pattern of the presence of miRNAs indicates their role in regulating the function of neurons. In other words, they can control vital pathways for proper brain function such as memory and learning, neuronal plasticity, synaptic function, neurogenesis, and brain growth (17). Some studies have shown that some miRNAs, such as 106b-5p/25-3p, miR-106a-5p/363-3p, and miR-17-5p/92-3p, have a main role in cortical growth (21, 22). One of the most plentiful miRNAs in the brain is miR-124-3p, which regulates axon growth in the retinal ganglion cells (23) and neurogenesis (24). A specific neuronal miRNA called miR-9-5p results in the proliferation and determination of the fate of neuronal progenitor cells (24, 25). MiR-9-5p also regulates neural migration and axonal growth (26, 27). In addition, miR-125-5p and Let-7b-5p have the main role in regulating astrocyte differentiation (28). But miR-138-5p and miR-338-5p have a chief role in the differentiation of oligodendrocytes (29, 30).

Small interfering RNAs, or siRNAs, were initially found in plants by recognizing their role as double-stranded RNAs in suppressing gene expression. The existence of such a mechanism was later confirmed in

mammals. The biogenesis mechanism of endogenous siRNAs is similar to miRNAs derived from dsRNA and processed in the cytosol by Dicer. This dsRNA binds to the RISC and AGO2 complexes, leaving the sense strand and maintaining only the antisense strand. This single-stranded RNA is directed to the target mRNA (17). The function of siRNAs is similar to that of miRNAs, but their mechanism of action is different. Just as siRNA sequences should exactly complement the target mRNA sequence, miRNAs can target multiple mRNAs (31). siRNAs are used as a molecular tool to inhibit gene expression under in vivo or in vitro conditions. Their role in controlling the expression of mammalian genes is still unclear. Additional researches are required to understand the role of these sncRNAs (17).

Piwi-associated RNAs, or piRNAs, are a group of sncRNAs that are about 24-30 nucleotides in length and have been shown to have an essential role in germ cells. The sequence of piRNAs between different species is not conserved. In addition, the mechanism of their synthesis in the cell is completely different from the previous two types. piRNAs are not initially synthesized as double-strands and don't need a Dicer molecule in their processing. piRNAs are also encoded from the repetitive intergenic elements such as transposable sequences as a large single-stranded precursor by polymerase II (17, 32). Two main mechanisms for piRNAs are known. 1- Primary biogenesis, which exists in both somatic cells such as neurons and germ cells; Secondary cycle or ping pong in which AGO3 binds to the piRNA antisense strand and targets the mobile elements that turn them silent. In addition, piRNAs are involved in sustaining genomic integrity, mRNA stability, and regulation of epigenetic processes (33-35).

Long non-coding RNAs

Long non-coding RNAs, or lncRNAs, are at least 200 nucleotides long and are usually generated by RNA Pol II or III. These ncRNAs are too structurally similar to mRNAs because they have a poly-A tail at the 3'UTR and a cap at the 5'UTR. They can also have alternative splicing, but lncRNAs are shorter than mRNAs and have less expression but show a higher tissue-specific expression pattern (36). LncRNAs are classified in various ways, including processing methods, their situational association with coding genes, and different nucleotide elements on the gene. They can be divided into four categories. 1- sense-intronic RNAs; 2- Long, non-coding RNA; 3- bidirectional RNAs; and 4- natural antisense transcripts (17).

The placement of various RNAs in different cell parts can be considered a regulatory mechanism. LncRNAs are less present in the nucleus than in other cellular organelles (37). LncRNAs in the nucleus are mostly found in paraspeckles, chromatin speckles, and nucleoli. The placement of LncRNAs in the cytoplasm is found in ribosomes, mitochondria, extracellular membranes, and exosomes. The placement patterns of lncRNAs are not unique and are commonly seen in various organelles and cell sections. The expression of this type of RNA is different in various tissues In other words, it is tissue-specific with a high expression in the central nervous system and its expression is controlled by age and position (17). Gene expression researches display that many lncRNAs have unique properties with respect to age and region of expression including the hippocampus, cerebellum, and cortex (38, 39). Also, these types of RNAs have higher expression specificity than the coding genes and determine the identity of the cell (40). The transcriptional location of lncRNAs on the genome affects their regulatory potentials. Many lncRNAs can impact the expression of adjacent genes, and sometimes the expression of genes is co-regulated (41). The co-regulation process occurs through the physical interactions of transcription machines and coding genes or chromatin remodeling (42). In addition to the cis-regulatory effect, lncRNAs can also regulate gene expression via trans. For example, they can alter chromatin forms at non-transcription sites or regulate the organization and structure of the nucleus. They can also regulate other RNA molecules and proteins (43).

Also, lncRNAs in the nucleus can be involved in gene silencing, RNA processing, translation, mRNA degradation, etc. (44). The mechanisms of the role of lncRNA in regulating gene expression are not well understood and more studies are required to comprehend it. These types of RNAs are associated with a large

number of pathological features and their expression level varies in disease conditions. Recently, the lncRNAs role in Alzheimer's has been highlighted (17).

The role of miRNA in the Alzheimer's pathogenesis

Evidence suggests that altering the miRNA pattern may alter the Alzheimer's disease risk. Some miRNAs contributed to regulating the gene expression involved in Alzheimer's, including BACE1 and APP. These alterations in the miRNAs profile are observed in Alzheimer's brain and cerebrospinal fluid and blood (45, 46). miRNAs are tested in vitro, in vivo, after-death Alzheimer's brain tissue, cerebrospinal fluid, and blood of Alzheimer's people. The level of most miRNAs in the Alzheimer's brain decreases. One report found that some miRNAs, including miR-219, miR-132, miR-128, miR-125b, and miR-124a, are found in large amounts in the fetal hippocampus, with major changes in the levels of some specific miRNAs in the Alzheimer's brain. In that study, miR-128 and miR-125b levels in Alzheimer's brain increased (47). Another study found that the levels of miR-107 were decreased in Alzheimer's. This miRNA may involve in the progression of Alzheimer's by interfering with the regulation of BACE1 gene expression (48). Some other researches show that in Alzheimer's brain the expression of some members of the miR-29a family decreased and consequently، the level of BACE1 increased (49, 50). In another study, the role of miRNAs in controlling APP gene expression was investigated. In that study, miR-106b, miR-17-5p, and miR-20a control the APP gene expression in the neuronal cell line. A substantial association was found between the aforementioned miRNAs and APP during neuronal differentiation and brain development. Due to the reduced expression of miR-106b in the Alzheimer's brain, it was proposed that these microRNAs contributed to the progress of Alzheimer's disease by influencing APP expression (51). The expression of miR-101 reduces in the cortex of the Alzheimer's brain, of course, the expression of some miRNAs, including miR-128 and miR-125b, increases in the Alzheimer's brain, which indicates their positive regulation. The miR-146b and miR-146a are also negatively and positively regulated in Alzheimer's. The expression of miR-9 can also increase or decrease in Alzheimer's. miR-219, miR-132, and miR-26a were also not observed in Alzheimer's disease (46).

It is very difficult to check for changes in the profile of miRNAs due to access to the living brain. But many studies can be done on samples such as blood or cerebrospinal fluid because these samples are relatively easy to access. miRNA profiles in Alzheimer's were altered in peripheral blood mononuclear cells. The expression of these miRNAs may be different in Alzheimer's patients carrying one or two APOE4 alleles (52). Also, the miR-590-3p expression in the monocytes of the analyzed Alzheimer's patients was reduced compared to the control subjects (53). miR-138 is abundant in the brain and is placed within dendritic branches and controls the size of dendrites of neurons in the hippocampus of rats (54). In Alzheimer's, MiR-15b is reduced in cerebrospinal fluid but not in the brain. In addition, studies show that miR-181c is reduced in Alzheimer's cerebrospinal fluid (45, 46).

Animal models of mice are commonly used for Alzheimer's studies. There are 1,184 known microRNAs in the genome of a mouse, 448 of them are expressed in the hippocampus, 23 of which are vastly expressed in the hippocampus and form about 83% of the total hippocampal miRNAs (55). It has been shown that miR-34c may be a biomarker for the onset of cognitive impairment in AD, and targeting this miRNA may be an appropriate treatment strategy (55). One study found that there was a decrease in the correlation between levels of mRNA and protein of the β-amyloid precursor protein-converting enzyme (BACE1) in the hippocampus of Alzheimer's mice. Subsequent studies also showed that miR-328 and miR-298 have binding sites downstream of BACE1 and could have regulatory effects on the expression of this protein in neurons in vitro (56). Pathological changes in the brain in Alzheimer's conditions are not completely reproducible in mice because there are differences between species in the severity and nature of Alzheimer's. In patients with AD, they show a large decrease in the cholinergic neurotransmitter system, the formation of NFTs, and a massive loss of neurons. However, fewer neuropathological changes are observed in APP transgenic mouse models (56). One study showed that miR-101 significantly regulates APP expression by affecting a control region in 3'-UTR and that direct transfer of miR-101

to HeLa cells reduces APP expression in humans (57). However, studies show that changes in the profile of miRNAs are observed in the progression of Alzheimer's disease. But more investigations are needed to determine the role of miRNAs in the pathophysiology of the disease.

lncRNAs contributed to the Alzheimer's pathogenesis

There are large numbers of lncRNAs in the human genome, about half of which are expressed in the brain. Disrupted expression of lncRNAs can be associated with some neurological disorders. The expression of many lncRNAs in 3xTg-AD mice was reported to be different from the control group (58, 59). BACE1-AS as a lncRNA has a role in Alzheimer's. BACE1-AS and BACE1 mRNAs are transcribed at the same location on human chromosome 11. The mRNA of BACE1 is generated from the sense strand and BACE1-AS mRNA is transcribed from the antisense strand. These two transcripts can complement each other and create a stable two-strand structure. This transcript is increased in the Alzheimer's brain compared to the control group (60). qPCR assessment revealed that the transcripts of BACE1-AS are more plentiful in the glial cells, the source of production of Aβ, rather than HCN1A cortical neurons. Also, increased BACE1-AS expression leads to increased BACE1 expression and beta-secretase regulation, which may explain the role of BACE1-AS in Alzheimer's pathology. In addition, the RNase protection assay showed that BACE1-AS and BACE1 could form a stable duplex to protect against destruction (60-62). Also, a study revealed that knockdown of BACE1-AS in an Alzheimer's mouse model could modulate beta-amyloid-related neurogenesis in the hippocampus (63).

One factor that decreases aging or Alzheimer's brain is the glial cell-derived neurotrophic factor or GDNF. The two non-coding transcripts, GDNFOS1 and GDNFOS2, are the GDNF complementary sequences, and their impaired expression could be involved in the progress of Alzheimer's (64, 65). BC200 lncRNA could regulate the gene expression in the level translation. BC200 levels decrease in normal aging in the cerebral cortex. But its expression in Alzheimer's brains increases (66). Also, single nucleotide polymorphisms can be correlated with changes in the risk of some diseases. Studies show that rs1333049, rs1063192, and rs3217992 polymorphisms in a lncRNA called ANRIL or CDKN2B-AS are associated with pathological features such as Alzheimer's, cardiovascular disease, and diabetes type 2 (62, 67, 68). In addition, one study found that 84 lncRNAs decreased in Alzheimer's, while 24 lncRNAs increased in Alzheimer's (69). n336934 is another lncRNA present in the mitochondrial genome associated with cholesterol homeostasis and plays a vital role in the formation of Aβ in Alzheimer's disease (70). Because mitochondria are inherited exclusively from the mother in humans, this mitochondrial lncRNA may be involved in maternal hereditary Alzheimer's (71, 73).

Nomerous lncRNAs have been recognized in which altered expression or mutations of them are involved in Alzheimer's pathogenesis. However, the exact mechanisms of involvement of lncRNAs in different stages of the disease have not been identified and further studies are needed. Accurate detection of the share of lncRNAs in Alzheimer's can identify them as therapeutic targets or biomarkers of Alzheimer's disease.

Conclusion

Alzheimer's disease is a progressive brain disorder that causes dementia in old age. Many environmental and genetic factors are involved in disease pathogenesis. Alterations in genes involved in the processing of beta-amyloid plaques or neurofibrillary tangles can increase the disease's risk disease's risk. Post-transcriptional mechanisms involved in gene expression regulation can also play a role in Alzheimer's pathogenesis. Non-coding RNAs, which commonly include miRNAs and lncRNAs, can play a role in regulating gene expression. miRNAs by interaction with 3′-UTR in target mRNAs can cause them to be silenced or even degraded. lncRNAs can also form stable complexes with mRNAs and affect their expression. It is very difficult to study these molecules in the brains of people with Alzheimer's because access to the living brain is usually difficult, but examining them in the blood and cerebrospinal fluid can be easier. Today, the diagnosis of Alzheimer's is made when severe brain damage has occurred, which poses a challenge in treating or preventing the progression of

the disease. Given that the expression profiles of many genes occur before the clinical signs of Alzheimer's, early detection of these changes can be a promising approach to providing treatment strategies.

References

1. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harbor Perspect Med 2011; 1(1): a006189. https://doi.org/10.1101/cshperspect.a006189

2. Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: back to the future. Neuron 2010; 68(2): 270-281. https://doi.org/10.1016/j.neuron.2010.10.013

3. El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. Nat Med 2007; 13(4): 432-438. https://doi.org/10.1038/nm1555

4. Wen L, Zhang Y, Yang B, Han F, Ebadi AG, Toughani M. Knockdown of Angiopoietin-like protein 4 suppresses the development of colorectal cancer. Cell Mol Biol 2020; 66(5): 117-124. https://doi.org/10.14715/cmb/2020.66.5.21

5. Hickman SE, Allison EK, El Khoury J. Microglial dysfunction and defective β-amyloid clearance pathways in aging Alzheimer's disease mice. J Neurosci 2008; 28(33): 8354-8360. https://doi.org/10.1523/JNEUROSCI.0616-08.2008

6. Sun Q, Xie N, Tang B, Li R, Shen Y. Alzheimer's disease: from genetic variants to the distinct pathological mechanisms. Front Mole Neurosci 2017; 10: 319. https://doi.org/10.3389/fnmol.2017.00319

7. Zaratiegui M, Irvine DV, Martienssen RA. Noncoding RNAs and gene silencing. Cell 2007; 128(4): 763-776. https://doi.org/10.1016/j.cell.2007.02.016

8. Yang M, Abdalrahman H, Sonia U, Mohammed AI, Vestine U, Wang M, Ebadi AG, Toughani M. The application of DNA molecular markers in the study of Codonopsis species genetic variation, a review. Cell Mol Biol 2020; 66(2): 23-30. https://doi.org/10.14715/cmb/2020.66.2.3

9. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrin 2018; 9: 402. https://doi.org/10.3389/fendo.2018.00402

10. Huang Y, Shen XJ, Zou Q, Wang SP, Tang SM, Zhang GZ. Biological functions of microRNAs: a review. J Physiol Biochem 2011; 67(1): 129-139. https://doi.org/10.1007/s13105-010-0050-6

11. Fiore R, Khudayberdiev S, Saba R, Schratt G. MicroRNA function in the nervous system. Prog Mole Biol Trans Sci 2011; 102: 47-100. https://doi.org/10.1016/B978-0-12-415795-8.00004-0

12. Maoz R, Garfinkel BP, Soreq H. Alzheimer's disease and ncRNAs. Neuroepigenom Age Dis 2017: 337-361. https://doi.org/10.1007/978-3-319-53889-1_18

13. Yang M, Shi D, Wang Y, Ebadi AG, Toughani M. Study on Interaction of Coomassie Brilliant Blue G-250 with Bovine Serum Albumin by Multispectroscopic. Int J Peptide Res Therap 2021; 27(1): 421-431. https://doi.org/10.1007/s10989-020-10096-6

14. Zusso M, Barbierato M, Facci L, Skaper SD, Giusti P. Neuroepigenetics and Alzheimer's disease: an update. J Alzheimer's Dis 2018; 64(3): 671-688. https://doi.org/10.3233/JAD-180259

15. Stoccoro A, Coppedè F. Role of epigenetics in Alzheimer's disease pathogenesis. Neurodegener Dis Manag 2018; 8(3): 181-193. https://doi.org/10.2217/nmt-2018-0004

16. Lauretti E, Dabrowski K, Praticò D. The neurobiology of non-coding RNAs and Alzheimer's disease pathogenesis: Pathways, mechanisms and translational opportunities. Age Res Rev 2021; 71: 101425. https://doi.org/10.1016/j.arr.2021.101425

17. Finotti A, Fabbri E, Lampronti I, Gasparello J, Borgatti M, Gambari R. MicroRNAs and long non-coding RNAs in genetic diseases. Mole Diag Ther 2019; 23(2): 155-171. https://doi.org/10.1007/s40291-018-0380-6

18. Quévillon Huberdeau M, Simard MJ. A guide to micro RNA-mediated gene silencing. FEBS J 2019; 286(4): 642-652. https://doi.org/10.1111/febs.14666

19. Zhang X, Xie K, Zhou H, Wu Y, Li C, Liu Y, Liu Z, Xu Q, Liu S, Xiao D, Tao Y. Role of non-coding RNAs and RNA modifiers in cancer therapy resistance. Mole Cancer 2020; 19(1): 1-26. https://doi.org/10.1186/s12943-020-01171-z

20. Natera-Naranjo O, Aschrafi A, Gioio AE, Kaplan BB. Identification and quantitative analyses of microRNAs located in the distal axons of sympathetic neurons. RNA 2010; 16: 1516-1529. https://doi.org/10.1261/rna.1833310

21. Suh MR, Lee Y, Kim JY, Kim SK, Moon SH, Lee JY, Cha KY, Chung HM, Yoon HS, Moon SY, Kim VN. Human embryonic stem cells express a unique set of microRNAs. Develop Biol 2004; 270(2): 488-498. https://doi.org/10.1016/j.ydbio.2004.02.019

22. Ventura A, Young AG, Winslow MM, Lintault L, Meissner A, Erkeland SJ, Newman J, Bronson RT, Crowley D, Stone JR, Jaenisch R. Targeted deletion reveals essential and overlapping functions of the miR-17~ 92 family of miRNA clusters. Cell 2008; 132(5): 875-886. https://doi.org/10.1016/j.cell.2008.02.019

23. He Y, Li HB, Li X, Zhou Y, Xia XB, Song WT. MiR-124 Promotes the Growth of Retinal Ganglion Cells Derived from Müller Cells. Cell Physiol Biochem 2018; 45: 973-983. https://doi.org/10.1159/000487292

24. Makeyev EV, Zhang J, Carrasco MA, Maniatis T. The MicroRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing. Mol Cell 2007; 27: 435-448. https://doi.org/10.1016/j.molcel.2007.07.015

25. Radhakrishnan B, Alwin Prem Anand A. Role of miRNA-9 in Brain Development. J Exp Neurosci 2016; 10: 101-120. https://doi.org/10.4137/JEN.S32843

26. Dajas-Bailador F, Bonev B, Garcez P, Stanley P, Guillemot F, Papalopulu N. microRNA-9 regulates axon extension and branching by targeting Map1b in mouse cortical neurons. Nat Neurosci 2012; 15: 697-699. https://doi.org/10.1038/nn.3082

27. Otaegi G, Pollock A, Hong J, Sun T. MicroRNA miR-9 modifies motor neuron columns by a tuning regulation of FoxP1 levels in developing spinal cords. J Neurosci 2011; 31: 809-818. https://doi.org/10.1523/JNEUROSCI.4330-10.2011

28. Shenoy A, Danial M, Blelloch RH. Let-7 and miR-125 cooperate to prime progenitors for astrogliogenesis. EMBO J 2015; 34: 1180-1194. https://doi.org/10.15252/embj.201489504

29. Lau P, Verrier JD, Nielsen JA, Johnson KR, Notterpek L, Hudson LD. Identification of dynamically regulated microRNA and mRNA networks in developing oligodendrocytes. J Neurosci 2008; 28: 11720-11730. https://doi.org/10.1523/JNEUROSCI.1932-08.2008

30. Douglas-Escobar M, Weiss MD. Biomarkers of brain injury in the premature infant. Front Neurol 2012; 3: 185. https://doi.org/10.3389/fneur.2012.00185

31. Lam JK, Chow MY, Zhang Y, Leung SW. siRNA Versus miRNA as Therapeutics for Gene Silencing. Mol Ther Nucleic Acids 2015; 4: e252. https://doi.org/10.1038/mtna.2015.23

32. Weick EM, Miska EA. piRNAs: from biogenesis to function. Development 2014; 141: 3458-3471. https://doi.org/10.1242/dev.094037

33. Grivna ST, Beyret E, Wang Z, Lin H. A novel class of small RNAs in mouse spermatogenic cells. Genes Dev 2006; 20: 1709-1714. https://doi.org/10.1101/gad.1434406

34. Ross RJ, Weiner MM, Lin H. PIWI proteins and PIWI-interacting RNAs in the soma. Nature 2014; 505: 353-359. https://doi.org/10.1038/nature12987

35. Czech B, Hannon GJ. One Loop to Rule Them All: The Ping-Pong Cycle and piRNA-Guided Silencing. Trends Biochem Sci 2016; 41: 324-337. https://doi.org/10.1016/j.tibs.2015.12.008

36. Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell 2013; 154: 26-46. https://doi.org/10.1016/j.cell.2013.06.020

37. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. Nat Struct Mol Biol 2013; 20: 300-307.

38. Lipovich L, Tarca AL, Cai J, Jia H, Chugani HT, Sterner KN, Grossman LI, Uddin M, Hof PR, Sherwood CC, Kuzawa CW. Developmental changes in the transcriptome of human cerebral cortex tissue: long noncoding RNA transcripts. Cerebral Cortex 2014; 24(6): 1451-1459. https://doi.org/10.1093/cercor/bhs414

39. Kadakkuzha BM, Liu XA, McCrate J, Shankar G, Rizzo V, Afinogenova A, Young B, Fallahi M, Carvalloza AC, Raveendra B, Puthanveettil SV. Transcriptome analyses of adult mouse brain reveal enrichment of lncRNAs in specific brain regions and neuronal populations. Front Cell Neurosci 2015; 9: 63. https://doi.org/10.3389/fncel.2015.00063

40. Molyneaux BJ, Goff LA, Brettler AC, Chen HH, Brown JR, Hrvatin S, Rinn JL, Arlotta P. DeCoN: genome-wide analysis of in vivo transcriptional dynamics during pyramidal neuron fate selection in neocortex. Neuron 2015; 85(2): 275-288. https://doi.org/10.1016/j.neuron.2014.12.024

41. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. Cell 2009; 136: 629-41. https://doi.org/10.1016/j.cell.2009.02.006

42. Nagano T, Fraser P. No-nonsense functions for long noncoding RNAs. Cell 2011; 145: 178-181. https://doi.org/10.1016/j.cell.2011.03.014

43. Kopp F, Mendell JT. Functional Classification and Experimental Dissection of Long Noncoding RNAs. Cell 2018; 172: 393-407. https://doi.org/10.1016/j.cell.2018.01.011

44. Li L, Zhuang Y, Zhao X, Li X. Long Non-coding RNA in Neuronal Development and Neurological Disorders. Front Genet 2018; 9: 744. https://doi.org/10.3389/fgene.2018.00744

45. Cogswell JP, Ward J, Taylor IA, Waters M, Shi Y, Cannon B, Kelnar K, Kemppainen J, Brown D, Chen C, Prinjha RK. Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. J Alzheimer's Dis 2008; 14(1): 27-41. https://doi.org/10.3233/JAD-2008-14103

46. Tan L, Yu JT, Hu N, Tan L. Non-coding RNAs in Alzheimer's disease. Mol Neurobiol 2013; 47: 382-393. https://doi.org/10.1007/s12035-012-8359-5

47. Lukiw WJ. Micro-RNA speciation in fetal, adult and Alzheimer's disease hippocampus. Neuroreport 2007; 18: 297-300. https://doi.org/10.1097/WNR.0b013e3280148e8b

48. Wang WX, Rajeev BW, Stromberg AJ, Ren N, Tang G, Huang Q, Rigoutsos I, Nelson PT. The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of β-site amyloid precursor protein-cleaving enzyme 1. J Neurosci 2008; 28(5): 1213-1223. https://doi.org/10.1523/JNEUROSCI.5065-07.2008

49. Zhu Y, Yang Y, Qu X, Yang P, Jiang L, He M. Pet/MRI in Alzheimer's disease: advances in the integrated PET/MRI system. Acta Med Mediter 2022; 38(1): 495-502.

50. Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, Kauppinen S, Delacourte A, De Strooper B. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/β-secretase expression. Proc Nat Acad Sci 2008; 105(17): 6415-6420. https://doi.org/10.1073/pnas.071026310

51. Shioya M, Obayashi S, Tabunoki H, Arima K, Saito Y, Ishida T, Satoh JI. Aberrant microRNA expression in the brains of neurodegenerative diseases: miR-29a decreased in Alzheimer disease brains targets neurone navigator 3. Neuropathol Appl Neurobiol 2010; 36(4): 320-330. https://doi.org/10.1111/j.1365-2990.2010.01076.x

52. Hébert SS, Horré K, Nicolaï L, Bergmans B, Papadopoulou AS, Delacourte A, De Strooper B. MicroRNA regulation of Alzheimer's Amyloid precursor protein expression. Neurobiol Dis 2009; 33(3): 422-428. https://doi.org/10.1016/j.nbd.2008.11.009

53. Wu XR, Gou L, Wang RJ, Sun FQ, Wang W, Huang W. Genetic polymorphism and genotype analysis of apoe4 and cr4 in patients with alzheimer's disease. Acta Med Mediter 2021; 37(5): 2301-2305. https://doi.org/10.19193/0393-6384_2021_5_357

54. Schipper HM, Maes OC, Chertkow HM, Wang E. MicroRNA expression in Alzheimer blood mononuclear cells. Gene Regul Syst Bio 2007; 1: 263-274. https://doi.org/10.4137/GRSB.S361

55. Villa C, Fenoglio C, De Riz M, Clerici F, Marcone A, Benussi L, Ghidoni R, Gallone S, Cortini F, Serpente M, Cantoni C. Role of hnRNP-A1 and miR-590-3p in neuronal death: genetics and expression analysis in patients with Alzheimer disease and frontotemporal lobar degeneration. Rejuven Res 2011; 14(3): 275-281. https://doi.org/10.1089/rej.2010.1123

56. Siegel G, Obernosterer G, Fiore R, Oehmen M, Bicker S, Christensen M, Khudayberdiev S, Leuschner PF, Busch CJ, Kane C, Hübel K. A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. Nat Cell Biol 2009; 11(6): 705-716. https://doi.org/10.1038/ncb1876

57. Zovoilis A, Agbemenyah HY, Agis-Balboa RC, Stilling RM, Edbauer D, Rao P, Farinelli L, Delalle I, Schmitt A, Falkai P, Bahari-Javan S. microRNA-34c is a novel target to treat dementias. EMBO J 2011; 30(20): 4299-4308. https://doi.org/10.1038/emboj.2011.327

58. Su W, Wang Z, Zhu Y, Zhang Y, Zhu L, Li L, Xia M, Li L. Genetic polymorphism of serum exosome-associated micrornas in patients with Alzheimers disease. Acta Med Mediter 2021; 37(4): 2365-2370. https://doi.org/10.19193/0393-6384_2021_4_369

59. Boissonneault V, Plante I, Rivest S, Provost P. MicroRNA-298 and microRNA-328 regulate expression of mouse beta-amyloid precursor protein-converting enzyme 1. J Biol Chem 2009; 284: 1971-1981. https://doi.org/10.1074/jbc.M807530200

60. Long JM, Lahiri DK. MicroRNA-101 downregulates Alzheimer's amyloid-β precursor protein levels in human cell cultures and is differentially expressed. Biochem Biophys Res Commun 2011; 404: 889-895. https://doi.org/10.1016/j.bbrc.2010.12.053

61. Li D, Zhang J, Li X, Chen Y, Yu F, Liu Q. Insights into lncRNAs in Alzheimer's disease mechanisms. RNA Biol 2021; 18: 1037-1047. https://doi.org/10.1080/15476286.2020.1788848

62. Lee DY, Moon J, Lee ST, Jung KH, Park DK, Yoo JS, Sunwoo JS, Byun JI, Shin JW, Jeon D, Jung KY. Distinct expression of long non-coding RNAs in an Alzheimer's disease model. J Alzheimer's Dis 2015; 45(3): 837-849. https://doi.org/10.3233/JAD-142919

63. Wu Q, He Y, Luo X. Value of urine ad-related neuronal thread protein combined with ptau protein detection in the early diagnosis Alzheimer disease. Acta Med Mediter 2021; 37(3): 1337-1341. https://doi.org/10.19193/0393-6384_2021_3_212

64. Faghihi MA, Modarresi F, Khalil AM, Wood DE, Sahagan BG, Morgan TE, Finch CE, St Laurent III G, Kenny PJ, Wahlestedt C. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of β-secretase. Nat Med 2008; 14(7): 723-730.

65. Busciglio J, Gabuzda DH, Matsudaira P, Yankner BA. Generation of beta-amyloid in the secretory pathway in neuronal and nonneuronal cells. Proc Natl Acad Sci USA 1993; 90: 2092-2096. https://doi.org/10.1073/pnas.90.5.209

66. Yan C, Miao M, Liu B, Qiu W, Chen M, Zhao L, Zou W. The value of Alzheimer's disease-associated neurofilament protein combined with ab1-42/p-tau-181 ratio for the diagnosis of Alzheimer's. Acta Med Mediter 2021; 37(3): 1653-1657. https://doi.org/10.19193/0393-6384_2021_3_264

67. Burd CE, Jeck WR, Liu Y, Sanoff HK, Wang Z, Sharpless NE. Expression of linear and novel circular forms of an INK4/ARF-associated non-coding RNA correlates with atherosclerosis risk. PLoS Genet 2010; 6: e1001233. https://doi.org/10.1371/journal.pgen.1001233

68. Zhou X, Xu J. Identification of Alzheimer's disease-associated long noncoding RNAs. Neurobiol Aging 2015; 36: 2925-2931. https://doi.org/10.1016/j.neurobiolaging.2015.07.015

69. Hannaoui S, Shim SY, Cheng YC, Corda E, Gilch S. Cholesterol balance in prion diseases and Alzheimer's disease. Viruses 2014; 6: 4505-4535. https://doi.org/10.3390/v6114505

70. Mosconi L, Berti V, Swerdlow RH, Pupi A, Duara R, de Leon M. Maternal transmission of Alzheimer's disease: prodromal metabolic phenotype and the search for genes. Hum Genom 2010; 4: 170-193. https://doi.org/10.1186/1479-7364-4-3-170

71. Chen H, He J. Correlation of plasma adiponectin and A. Deposition-related indexes with VEGF, FOL, and VITB12 in patients with Alzheimer's disease. Acta Med Mediter 2021; 37(2): 891-895. https://doi.org/10.19193/0393-6384_2021_2_135

72. Yin G, Wang F, Hu X, Fu A, Yao C. Efficacy and Safety Analysis of Risperidone and rTMS Drugs in the Treatment of Alzheimer's Disease with Psychobehavioral Symptoms. Lat Am J Pharm 2022; 41(6): 1075-1079.

73. Liu Z, Wu X, Yang S. Two Mixed-Ligand Coordination Polymers: Treatment and Nursing Application Values on Alzheimer's Disease. Lat Am J Pharm 2021; 40(10): 2544-2549.

How to cite this paper:

Maavaeian A, Mohebi H, Ahmed K. Non-coding RNAs and their role in Alzheimer's pathogenesis. Cent Asian J Med Pharm Sci Innov 2022; 2(3): 86-97.