Alzheimer's Disease & Treatment

Chapter 5

miRNAs as Biological Markers in the Diagnosis and Treatment of Alzheimer's Disease

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Abstract

Although the diagnosis and treatment studies that can be developed by clarifying the pathology of Alzheimer's disease (AD), which is one of the most common dementia in the world, have been studied intensively, an explicit result cannot be obtained. With new technologies developing every day, new approaches are being tried. The investigation of miRNA as a biomarker in the diagnosis of AD has recently started in this context. miRNAs are thought to have significant effects on the pathology of neural functions and hence neurological diseases. The ideal candidate for being a biomarker is a high rate of miRNAs in the brain and the circular system, and the key roles they play in the pathology of neurodegenerative diseases. In this chapter, the possible use of miRNAs as biological markers in AD is discussed.

Keywords: Alzheimer's disease; miRNA; Biological marker

1. Alzheimer's disease

Alzheimer's disease (AD), diagnosed by Alois Alzheimer's in the 1900s, is a progressive neurodegenerative disease, which is the most common type of dementia, over the age of 65 years [1]. Neurodegenerative diseases caused by the interaction and combination of genetic, epigenetic and environmental factors are generally defined as an abnormal accumulation of proteins [2].

The disease reveals itself in specific regions of the brain such as the hippocampus, amygdala, temporal cortex and frontal cortex [2] which are responsible for memory and cognitive function. Neural losses and atrophy begin in these regions due to protein accumulation [3]. Several definitions have been made in AD to understand the clinical progression of the disease better.

There are two main pathological features that have not changed since the discovery of the disease; amyloid plaques and neurofibrillary tangles. Disease characteristics including these pathologies have been associated with many genes as well as environmental factors. However, in order to solve the complex structure of this multifactorial disease, studies on diagnosis and treatment are not sufficient.

Some classifications have been made to facilitate diagnosis and research into this complex disease. One of them is The Braak and Braak's classification which is the hypothesis that the disease appears to be spread over a long period and clinical symptoms begin to be observed in the final stages. Apart from the Braak and Braak's classification, there are several criteria and classifications published by institutions such as the National Institute of Neurological and Communicative Disorders (NINCDS) [4]. However, this classification was preferred for this chapter because it has a more physiological and pathological basis. In all these classifications and diagnostic criteria, the sensitivity and specificity of the diagnosis are 70-80 % [5] Besides, this classification has been assessed the degree of cognitive impairment with Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) [6,7].

2. AD Pathogenesis

In the nervous system, some of the cellular changes with aging, such as oxidative stress, mitochondrial deterioration, and epigenetic modification, can lead to neurodegenerative diseases [8].

When the pathogenesis of the disease is examined, it has been found that there is abnormal protein accumulation consisting of intracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques (APs) (**Figure 1**) [1]. Abnormal protein accumulation disrupts cellular homeostasis, and neuronal degeneration begins from the hippocampal region of the brain

and continues to spread to the isocortex [9].

Although the pathophysiology of APs and NFTs were useful in the pathogenesis of AD, later studies have shown that neurofibrils, dystrophic neurites and Hirano bodies may also be associated with the disease [3].

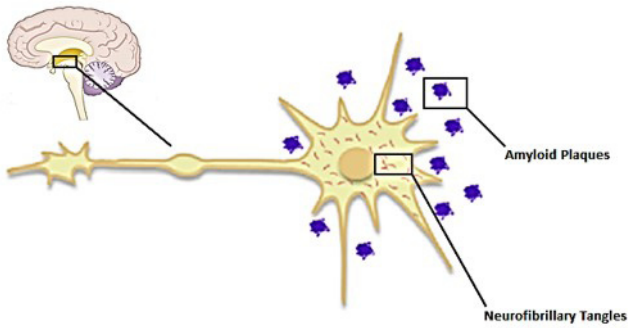

Figure 1: Two main causes in AD pathogenesis; amyloid plaques and neurofibrillary tangles

3. Related Genes in AD

The disease is classified into two different stages as early and late-onset AD. Under this categorization, several genes associated with the disease have been identified [10]. Although early and late-onset AD resembles each other, it has been found they were separated from each other in the genotypic levels. To give an example, while mutations in amyloid precursor protein (APP), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes are responsible for early-onset AD, the most important effect of apolipoprotein E (*APOE*) mutations are seen in late-onset AD [11].

Enzymatic cutting of APP which is important for the functionality of this protein happens in two ways; the amyloidogenic pathway which produces toxic forms of Aβ peptides and the non-amyloidogenic pathway that provides a beneficial neurotrophic effect. In the non-amyloidogenic pathway, the cleavage of APP occurs by α-secretase, which is produced by the p3 peptide and it creates soluble fragments form [12]. In quantity and function, the most important cleavage in APP is occurring by α-secretase. As a result of this cleavage, ectodomain part of APPsα is released. The remaining carboxy-terminal of APP-CTFα is processed by γ-secretase [13,14].

Mutations in beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) which is a membrane-dependent aspartyl protease and one of the known β-secretase, PSEN1 and PSEN2 affect β-secretase and γ-secretase activity [15,16]. Mutations occurred at the 3'-untranslated region (UTR) end of APP's mRNA are thought to play an essential role in the disease by causing deterioration in miRNA regulation [16]. In this case, APP is directed to the amyloidogenic pathway and cut by β- and γ-secretase. Consequently, the peptides accumulate by forming insoluble aggregates cause neurodegenerative diseases such as AD. β-secretase cleavage causes APPsβ to release from ectodomain. Then the remaining APP carboxy-terminal

fragment (APP-CFT) is cleaved by γ-secretase to release Aβ peptides and APP intracellular domain (AICD) (Figure 2). Although the biological functions of APPsβ, Aβ, and AICD are not fully understood; Aβ release has been associated with synaptic activity and suppression of stimulating synaptic conduction in neurons. Aβ toxicity appears to cause morphological changes in cells. In addition to morphological changes; *in vitro* and *in vivo* studies have shown that amyloid toxicity kills neurons [13,17]. Therefore, because Aβ monomers turn into toxic oligomers to form plaques; Abnormal accumulation of Aβ in the brain is an essential pathological marker for AD [18,19].

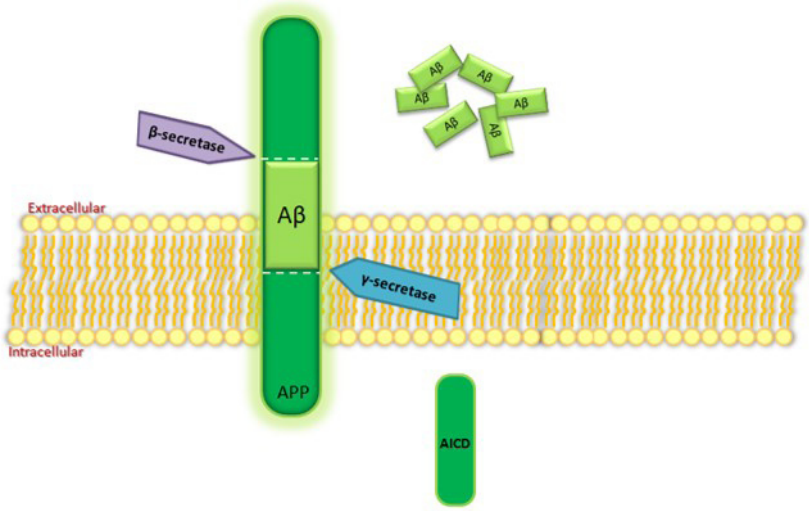

Figure 2: Amyloidogenic pathway. APP cleavage respectively by β- and γ-secretase

There are some forms of amyloid beta, such as 42, 40, 35 amino acids in length. Aβ42 which is the most toxic form of Aβ is formed by the cleavage of APP by β- and γ-secretase like the other amyloid forms. This 42-amino-acid-insoluble peptide accumulates in the brain and shows toxicity on cells [12]. In the light of in *vitro* studies conducted in 1989-1990, it has been reported that the Aβ aggregates show some degree of neurotrophic effects. However, in 1990, Yanker et al. demonstrated that an abnormal increase of Aβ aggregates might be neurotoxic. The amyloid-beta deposition may result in overproduction of reactive oxygen species that may cause synaptic deterioration and neuronal loss; disrupts calcium hemostasis, and increases oxidative stress. Apoptosis or necrosis is also induced in cells due to the Aβ concentration [20, 21].

Besides genes that have been clarified to be directly associated with the disease, many other genes are thought to be effective in the pathogenesis of the disease. One of these, triggered receptor expressed on myeloid cells 2 (*TREM2*), which is expressed from the plasma membrane of microglia, plays a role in the formation of an immune response in the central nervous system by increasing inflammatory stoking production [22]. Ephrin type-B2 receptor (*EPHB2*) encodes a transmembrane glycoprotein that is a member of receptor tyrosine kinases and ionotropic glutamate receptor AMPA type subunit 2 (*GLUA2*) are the other genes which play an important role in the regulation of synaptic function [23].

4. Diagnostic and Therapeutic Techniques for AD

Today, the diagnosis of the disease is made by examining the clinical symptoms that appear in the later stages of the disease. The ideal criterion for diagnosing patients is to diagnose as early as possible without symptoms. Unfortunately, even though intensive studies on non-invasive early diagnosis are prominent, for now, adequate early diagnosis cannot be seen [24,25] and this is about the complex nature of AD, a multifactorial disease [20].

Nowadays, even if there are diagnostic methods such as positron emission tomography (PET) scanning, magnetic resonance (MR) imaging, biomarkers, gene detection, and cognitive testing, it is frequently confused with other types of dementia and thus makes it difficult to reach a definitive diagnosis [1,3,26]. Also, methods such as retinal imaging of amyloid-beta or alterations in a patient's sense of smell are also used. However, with the exception of biomarker and gene detection techniques, it can be measured and observed by the emergence of clinical symptoms. Nowadays, these tests and examinations are performed to diagnose at the clinical stage, but Clinical cases have shown that even after these diagnostic parameters, mistakes can be seen. No miRNA biomarker screening has yet been performed in the clinic. Screening of miRNAs that play such an important role in the AD mechanism will be an important parameter for diagnosis and treatment.

Although it is not possible to treat Alzheimer's disease, symptomatic treatment approaches are applied in Alzheimer's patients. Cholinergic therapy such as donepezil, rivastigmine, and treatments based on the use of glutamate - N-methyl-D-aspartate (NMDA) receptor antagonists are applied. It reduces the acetylcholine concentration distributed to the cortex and hippocampus by cholinergic treatment [27,28].

5. miRNA

Micro ribonucleic acids (miRNAs) are short, endogenous non-coding RNAs, which are key roles for survival and neuronal functions. They have an essential role as regulators in the post-transcriptional phase [20]. The mature miRNA is a single chain RNA molecule of about 20-25 nucleotides. Many miRNAs have been shown to be important in neuropathology by affecting AD-associated proteins [29]. miRNAs, which are transcribed as a premature RNA (pre-miRNA) in the nucleus and matured as a result of the Ribonuclease III Dicer fraction in the cytoplasm; mediates mRNA degradation and suppression. Actually, these non-coding short RNAs act as regulators in intracellular gene expression [30]. Mature miRNAs recognize the 3'-UTR of mRNA with specific binding [30,31]. miRNAs have important roles in Alzheimer's disease. To give an example in this context, researchers find out 3'-UTR of APP which is one of the genes involved in AD, has a close relationship with the occurrence of the disease. Zhou et al. showed that in the case of AD, *APP* has single nucleotide polymorphism in the 3'-UTR [31]. Through their important role in silencing gene expression, they provide a promising tar-

get for the regulation of cellular processes [8].

5.1. miRNA biogenesis

miRNA biogenesis begins by transcribing the primary miRNA (pri-miRNA) transcript from the genes encoding miRNA in the nucleus. Primary miRNA is formed by the enzymatic cleavage of Drosha and DGCR8 protein, leading to miRNA (pre-miRNA). At the end of this step, they transported to the cytoplasm by Exportin-5 and Ran-GTP proteins and cut with cytoplasmic proteins Dicer and TRBP to form miRNA duplexes. This duplex structure is opened by helicase to form mature miRNAs. Mature miRNAs form the RISC complex with the Ago2 protein, thereby targeting the 3'-UTR of the mRNA and suppressing its translation (Figure 3) [8]. miRNAs play a key role in the coding of post-transcriptional regulatory proteins. They regulate gene expression by binding to mRNA and repressing and/or degrading at the translational stage. Irregularity in miRNAs; It is supported by increasing evidence that it causes changes in the expression of disease-related genes, thereby leading to the onset and/or progression of various diseases [18].

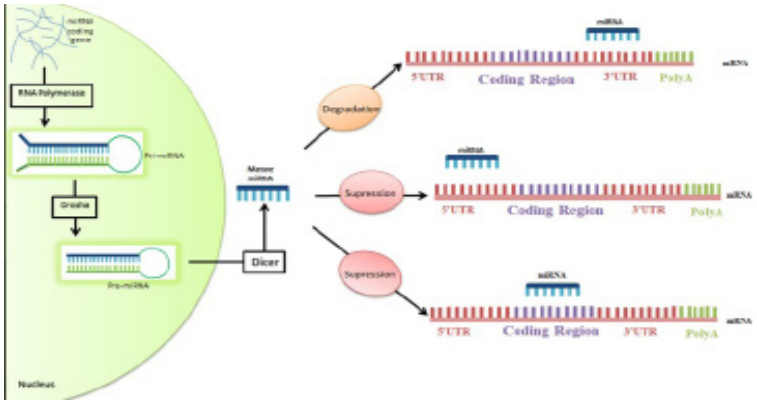

Figure 3: miRNA biogenesis and function

5.2. miRNA in AD

Given the key roles, miRNAs play in neural differentiation, synaptogenesis, and plasticity; they are highly expressed in the brain [32].

Although extended research has been conducted for Alzheimer's disease, we do not have a technique to provide a definitive diagnosis or any drug to prevent the disease [8]. Therefore, researchers have focused on studies to find non-invasive diagnostic tests such as miRNA [33].

Pathological changes in the brains of AD's patients begin to occur a long time before the clinical symptoms are observed and there is no effective treatment against this abnormality. Today, only symptomatic treatments are used. The lack of specific diagnostic biomarkers is one of the major factors in the early detection of the disease. Therefore, biological markers are of great importance in the early diagnosis of Alzheimer's disease. The ideal biological marker should be specific and easy to measure, defining the neurodegenerative process before cogni-

tive consciousness begins to weaken [34,35]. For example, Aβ42 and Tau proteins were identified as cerebrospinal biomarkers and Aβ oligomers are also candidates for synaptic markers [35]. But these biomarkers are not related to the early stages of the disease and the technique which is used to sampling is also one of the invasive detection methods.

miRNA is thought to be involved in neuronal development, differentiation, and synaptic plasticity of neurons. Additionally, disruption in miRNAs is thought to cause diseases such as central nervous system diseases, Alzheimer's and Huntington's disease. When the studies on the subject are examined, it is thought that because of the dysregulation of some miRNAs in Alzheimer's disease, this anomaly may play a role in the pathology of the disease and therefore miRNAs may be non-invasive and sensitive biological markers [36].

It is known that miRNAs are expressed at high rates in neural systems and have important roles in neuropathology [18,20,29]. AD is a slowly progressive and age-dependent neurodegenerative disease. Diagnosis and treatment studies have been intensified considering the increasing frequency of AD day by day [30]. These studies show that miRNA studies have gained popularity in the diagnosis and treatment process [30]. For example, some findings have shown that miR-30b influences the expression of synaptic integrity genes, and increases Aβ42 by NF-κB signaling, especially if we are talking about AD [23]. Also, it has been shown reduced miRNAs that target the BACE1 gene, which is effective on amyloid plaque formation, raised in the case of AD [23]. In this regard, upregulated miRNAs that affect the expression of BACE1 will be the first step in the treatment and also the examination of miRNAs in the BACE1 pathway may open the door for the diagnosis. miRNA studies are thought to contribute to the diagnosis and treatment process, as well as help to understand the mechanism of the disease [30].

miRNA expression is tissue- or cell-specific. Besides, the disease and its specificity to the stages of the disease make miRNAs exciting and unique. Other advantages of miRNA are common in CSF, brain, and blood circulation [9]. Since miRNAs are associated with blood and CSF, it is an important parameter, especially since there is not enough biomarker at the diagnosis of AD [38]. Given all the advantages, it is quite plausible that these non-coding RNAs can be used in the diagnosis of neurodegenerative diseases. There are some studies that showed miRNAs up or downregulated in the case of AD and can be used as a biomarker to diagnosis of this disease (Table 1).

Non-coding RNAs have been observed in blood, CSF, and brain tissues as well [31]. Some studies show that the early and late stages of AD occur at sufficient levels for biological markers in peripheral blood [37]. But, while some miRNAs have been identified as potential biomarkers in the literature, some miRNAs have been shown to produce conflicting results.

So far, several library studies have been conducted on samples from human tissues re-

lated to miRNAs involved in processes and diseases. The results from these studies became clearer after AD's *in vitro* and *in vivo* modeling studies. These preliminary studies have made it easier to study with human tissues or biological fluids samples. In studies with brain tissue and CSF samples, pathways in which miRNAs are effective and treatment approaches have revealed by comparing AD patients and healthy individuals.

6. Brain Tissue

Brain tissue samples are frequently studied in neurodegenerative diseases *in vivo*. One of the primary reasons for this, to obtain the most accurate results in parallel with the pathology of the disease. miR-132 showed significant down-regulation when examined samples from different brain tissues that are related to AD [39–44]. In the studies carried out by taking samples from the brain, it is seen that the hippocampal region is primarily used, but the temporal and frontotemporal cortex is also used. [23,39–43]. Due to changes in gyrus and cerebellum in later stages of the disease, in addition to the hippocampus, Cogswell et al. examined these regions [39]. Studies in the brain tissues are advantageous in terms of diagnosis since they can show changes in miRNAs in the early or late stages of the disease. It also takes a step closer to the treatment of the disease on the pathways affected by miRNAs [23,39–43].

7. Cerebrospinal fluid (CSF)

Researches on CSF for finding a biomarker is got more attention than other regions' research as of location. These studies are focused on hyperphosphorylated-Tau and Aβ, which are the primary symptoms of AD. It is also possible to carry out the analysis of genes that are determined as genetic risk other than protein from CSF. It can be collected by invasive methods such as lumbar puncture for this protein and gene analysis reflecting the pathology of AD. Even if it is high accuracy, being invasive is one of the disadvantages of these studies [45].

8. Blood

Analyzes which are planned to be taken as examples from blood are preferred for early diagnosis due to their non-invasive and ease of application. Thus, blood analyzes are prioritized to investigate the early diagnostic biomarkers and to investigate the epigenetic mechanisms effective in the disease [45]. When the studies are analyzed, it can be seen that blood samples are collected from the people diagnosed with AD, and their miRNAs are isolated. The analysis is then performed using sequencing techniques in accordance with literature and screened miRNA libraries in general. Given the circulating involvement of miRNAs, it is an important parameter that these molecules are associated with diagnostic screening and disease. Given the circulating involvement of miRNAs, diagnostic screening and association with the disease is an important parameter. In this way, it will be possible to diagnose the early stages of the disease without harming the patient [46–48].

Table 1: Some miRNAs studied in association with AD

miRNA	Status (up- and down-regulation)	Regions can be detected	Associated genes	Ref.
miR-181c	↓	Blood	-	(48)
miR-29b	↓	Blood	BACE1	(49)
miR-342	↓	Blood	-	(46,47)
miR-112	↑	Blood	-	(52)
miR-161	↑	Blood	-	(52)
miR-125b	↓	-	TREM2	(50)
miR-132	↓	Brain tissue	APOE4	(39–44)
miR-30b	↑	Brain tissue	SIRT1, ephB2,GluA2	(23)
miR-328	↓	Brain tissue	BACE1	(51)
miR-298	↓	Brain tissue	BACE1	(51)
miR-107	↓	Serum	BACE1	(53,54)
miR-101-3p	↓	Serum	APP	(31)
miR-144-3p	↓	Serum	APP/ADAM10	(31)
miR-153-3p	↓	Serum	APP	(31)
miR-381-3p	↓	Serum	APP	(31)
miR-151a	↑	Serum	-	(52)
let-7d	↑	Serum	-	(52,55)

9. Clinical trials in AD

Clinical trials are searched on clinicaltrails.com, which is a website where the clinical trials are collected and recorded; the lack of studies is a disappointment. Although the studies do not specifically focus on AD and the desired efficiency cannot be obtained in the results [56]. For example, the study of mir107 associated with brain structure phenotype and BACE1 in AD demonstrated the linked to the expression of BACE1 mRNA and mir107 in plasma [57]. Although this study unravels another node from the complex structure of the disease, it is not very efficient for the diagnosis and treatment process.

10. Conclusion

Considering the incidence of AD, in the light of increasing studies, using miRNAs as a biomarker is advisable. Furthermore, their high expression in the neurological system can be seen as an advantage as these RNAs play a key role as regulators. For instance, reviewed the studies, many miRNAs have been shown to be effective in silencing, up-regulating, or down-regulating the BACE1 gene involved in amyloid plaque formation. Considering the amyloid cascade hypothesis; miRNA research is an indispensable part of the diagnosis and treatment of the disease.

The inadequacy of the diagnosis and treatment of AD, which has been heavily researched,

especially since it affects the vast majority of people over the age of 65, presents us with an annoying picture. Research on diagnosis and treatment allows us to understand the mechanism of the disease and then take us one step closer to the cure. In the diagnosis and treatment studies conducted on behalf of the disease, researchers concentrate on investigating techniques that will not harm the patient as much as possible. Therefore, miRNAs are a marvelous choice for research both in diagnosis and treatment. One of the advantages of miRNA research is that they are obtained from direct brain tissue as well as being highly expressed in blood circulation. In addition to all these, they also have a more advantageous role in the mechanism of a complex disease such as AD.

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