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MiR-107 Activates NF- κ B versus A β Analysis of the regulatory effect of 1-42 induced apoptosis in Alzheimer's disease cells

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ABSTRACT

Alzheimer's disease (AD) is one of the acute degenerative diseases of the brain that occurs in the central nervous system. This disease is caused by the abnormal deposition of insoluble plaques and peptide amyloid beta (Aβ), the formation of nodules, and synaptic disorder. The formation of these nodes disrupts the functioning of neural circuits and changes in behavioral response due to the activation of neurotransmitter receptors. Research in recent years has shown that microRNAs play an effective role in Alzheimer's disease and neurotransmitter factors. Recently, miR-107 is effective in the pathology of Alzheimer's disease (AD) through the regulation of the NF-κB signaling pathway. Experiments conducted using the dual luciferase method and western blot analysis also showed that miR-107 in primary neurons affects neurotransmitter factors in Alzheimer's disease through the regulation of the NF-κB signaling pathway. The results showed that the reduction of miR-107 expression through the regulation of the NF-κB signaling pathway leads to the suppression of cell apoptosis in Alzheimer's patients. On the other hand, increasing the expression of miR-107 leads to increasing the breaking process of Amyloid precursor protein (APP). This factor increases the production of amyloid beta (Aβ) peptide plaques and increases the expression of the BACE1 gene, which ultimately leads to the induction of apoptosis and induction of Alzheimer's disease.

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Introduction

Alzheimer's disease (AD) is one of the most common dementia and neurodegenerative diseases that occur in the central nervous system and is irreversible. Pathologically, the most important causes of Alzheimer's disease are two proteins, Amyloid-beta (Aβ) and Tau Protein. These two factors lead to the deposition of peptide and amyloid beta (Aβ) of aging amyloid plaques and interneuron tangles in the extracellular environment and thus play a major role in Alzheimer's disease (1). Amyloid beta (Aβ) also has many physiological functions in the brain, but in general, its excessive production increases the accumulation of this protein and amyloid plaques, which is harmful to the activity of neurons and leads to synaptic disorder and neuronal death. Tau protein is also hyper-phosphorylated in Alzheimer's patients, which leads to the production of insoluble aggregates and tangled coils inside neurons. Finally, the structure of microtubules and then the cell skeleton of the neuron will be destroyed, especially in the axons and dendrites, and finally, the structure of synapses and the transmission of messages between neurons will suffer serious damage (2). Amyloid-beta (Aβ) and Tau Proteins have a mutual relationship, and the increase of one of them leads to the increase of the other factor (3-4). Several reports show that several factors, including changes in the expression of non-coding RNAs, act as one of the main factors in the changes in expression of Amyloid beta (Aβ) and Tau Protein. Recent molecular research has shown that non-coding RNAs are involved in the diagnosis, control of progress, and treatment of many diseases, including cardiovascular diseases (5), types of cancer (metastasis) (6), mental disorders (Alzheimer's) (7), and multiple sclerosis (MS) (8).

MicroRNAs (miRNAs) are short (20-24 nt) non-coding RNAs that are involved in the post-transcriptional regulation of gene expression in multicellular organisms by affecting both the stability and translation of mRNAs. MiRNAs are transcribed by RNA polymerase II as part of capped and polyadenylated primary transcripts (pri-miRNAs) that can be either protein-coding or non-coding (9-10). MicroRNAs regulate gene expression at the RNA level. MicroRNAs are involved in various cellular processes, including development, cell division, cell signaling, and cell growth, and generally play an effective role in the cell cycle and control of physiological processes and cell pathology (11). Table 1 shows the effective genes in Alzheimer's disease along with related microRNAs and their role. Many of these microRNAs are effective in different molecular mechanisms, neurotoxicity, synaptic disorder, production, storage, or removal of amyloid beta (Aβ) (12-30).

Materials and Methods

First, the sequence of MiR-107 (Accession number:

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Table 1. The name and role of the main genes involved in the pathogenesis of Alzheimer's disease and the microRNAs reported for these genes.

Gene name	Related microRNAs	The role of target gene protein in Alzheimer's disease
APP	miR-200-b, miR-106a, miR-106b, miR-520c, miR-20a, miR-17-5p, miR-153, miR-16, miR-101	Overexpression of amyloid-beta precursor protein causes more amyloid-beta production, and this process leads to neurotoxicity and synaptic disorder (12).
BACE1	miR-339-5p, miR-29a/b, miR-29c, miR-107, miR-298, miR-328, miR-195, miR-124, miR-135a, miR-135b, miR-186	The process of breaking down APP and producing amyloid beta (Aβ) (13)
Tau	miR-132	Phosphorylation of tau (14)
Fyn	miR-106-b	Phosphorylation of tau (15)
PTPN1	miR-124	It plays a role in synaptic dysfunction and Suppression of PTPN1 (16)
ITPKB	miR-132	It plays a role in the accumulation of amyloid beta (Aβ) (17)
Sirt1	miR-132	De-acetylating various protein targets has a protective effect against Alzheimer's disease (18)
NOS1	miR-132	It is involved in the pathway of tau phosphorylation (19)
PTEN	miR-132, miR-212	It plays a role in beta-amyloid neurotoxicity (20)
FOXO3	miR-132, miR-212	It plays a role in beta-amyloid neurotoxicity (20)
TNFAIP1	miR-137	It plays a role in beta-amyloid neurotoxicity (21)
BDNF	miR-10a	Changes in BDNF expression in specific neuronal subtypes (22)
UCHL1	miR-922	Decreased synaptic functions (23)
RARA	miR-138	Phosphorylation of tau (24)
SNX6	miR-98-5p	Increase of Aβ42, Aβ40 (25)
ROCK1	miR-146a	Phosphorylation of tau (26)
VAMP2	miR-34C	Decreased synaptic functions (27)
SPHK1	miR-125b	Abnormal phagocytosis (28)
VAV1	miR-330	Oxidative stress and mitochondrial dysfunction (29)
ApoE	miR-1908	Reduction of amyloid beta (Aβ) accumulation (30)

MI0000114) was obtained from the NCBI database. Then the exact location of this microRNA was determined using the UCSC database, then the ProtScale database was used to obtain the molecular weight and isoelectric point of MiR-107. Cell comparison and analysis of genes effective in microRNAs were analyzed by the Human Protein Atlas OMIM database. Finally, the Alliance of Genome Resources database was used to investigate the expression of MiR-107 in different body organs and western blot analysis.

Results

MiR-107 is one of the most important types of microRNAs that play an important role in the induction of apoptosis and Alzheimer's disease. Table 2 shows the specific characteristics of this microRNA along with molecular weight and isoelectric point (31).

BACE1 encodes a gene from the peptidase A1 family of aspartic proteases. This protease catalyzes the first step in the formation of the beta-amyloid peptide from the amyloid precursor protein. Beta-amyloid peptides are the main component of beta-amyloid plaques that accumulate in the brains of human Alzheimer's patients (32). The MIR107 factor leads to an increase in the expression of this gene through the NF-κB signaling pathway and breaking APP Amyloid precursor protein. Also, the inflammatory mechanisms of the NF-κB signaling pathway in the brain are activated in response to Aβ plaques. Several reports indicate that T cells are also activated in patients with AD and that these cells are present both in the environment and infiltration in the brain. Also, inhibiting the NF-κB-related SYK signaling pathway suppresses cell apoptosis through the reduction of MIR107 expression (33). The schematic Figure 1 shows the effect of MIR107 on the amyloid genic pathways.

Nuclear factor-kB (NF-kB)

Nuclear factor NF-κB is a family of transcription fac-

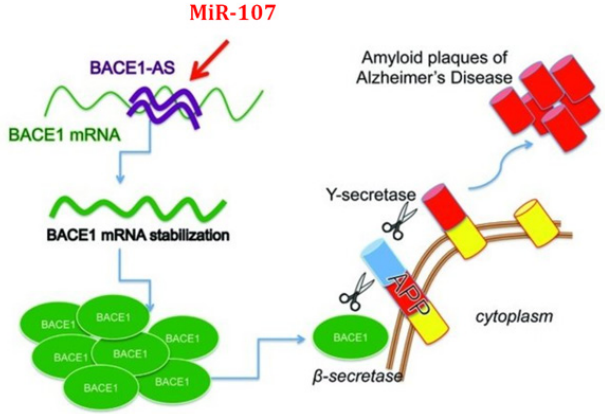

Figure 1. Schematic of the effect of MIR107 on amyloid genic pathways (33).

Table 2. MiR-107 exclusive features.

Name	MIR107 microRNA 107
ORGANISM	Homo sapiens (Human)
Accession number	MI0000114
GenBank	AJ550401.1
Accession number	AGCAGCATTGTACAGGGCTATCA
Gene ID	406901
Chromosome	10
Cytogenetic location	10q23.31
Chromosome location bp	89592747-89592827
nucleotide length	23bp
Biotype	ncRNA gene
Molecular weight (Da)	1879.10
Isoelectric point	5.53
Total Exon	1

tors that plays an important role in inflammation, immunity, cell proliferation, differentiation, and survival. NF-κB activation depends on proteasome degradation caused by inhibitory phosphorylation. NF-κB acts as a central mediator of the immune and inflammatory systems and plays a role in stress response and regulation of cell proliferation and apoptosis. In general, the corresponding NF-κB target genes allow organisms to effectively respond to these environmental changes. Most effects of the NF-κB signaling pathway are related to the induction of kinase and phosphorylation. In this pathway, protein kinase inhibitors IkBs play an important role and the combination of these factors ultimately leads to the activation of dimers such as p52-RelB. (MIR107) microRNA 107 is one of the types of microRNAs that affect the NF-κB signaling pathway through phosphorylation (Figure 2) (34). In the last two decades, tremendous progress has been made in discovering the details that have made it possible to understand the general principles of signal transduction and gene regulation.

Examination of MiR-107 expression

The analysis of gene expression in the anatomy of *Mus musculus* and *Homo sapiens* showed that the expression

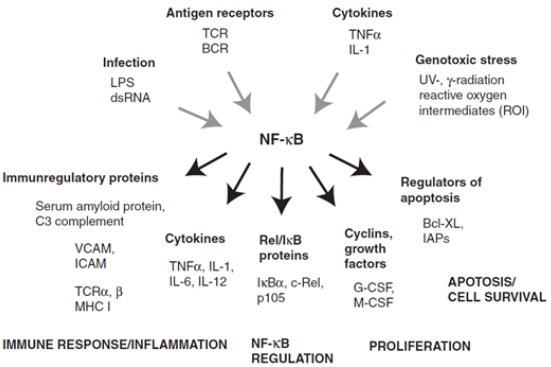

Figure 2. NF-kB stimuli and target genes (34).

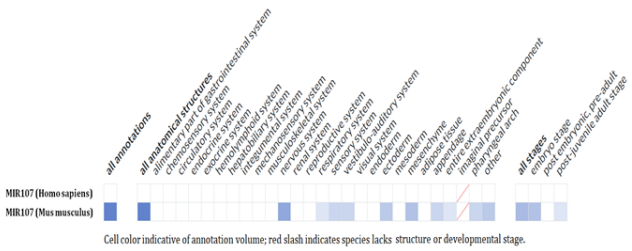

Figure 3. The expression level of MiR-107 in different organs in Mus musculus and Homo sapiens.

level of MiR-107 is higher in the nervous system, respiratory system, vestibule-auditory system, Mesenchyme, ectoderm, Appendage, pharyngeal arch, entire extra embryonic component, and sensory system and is seen in all stages, especially in the embryo stage and post-juvenile adult stage (Figure 3).

Western blot analysis

Figure 4 shows a Western blot analysis of BACE-1 in human brain tissue (Alzheimer's disease hippocampus). PVDF Membrane was probed with 2 µg/mL of Mouse Anti-Human/Mouse BACE-1 Ectodomain Monoclonal Antibody (Catalog MAB931) followed by HRP-conjugated Anti-Mouse IgG Secondary Antibody (Catalog HAF007). The resulting Specific bands for BACE-1 were detected at around 60 and 70 kDa (as indicated) (Figure 4). This test was performed under reducing conditions and using the Immunoblot buffer in Table 3.

Discussion

Currently, 850,000 people in the UK are suffering from Alzheimer's disease, which is expected to increase to 1.1 million people by 2025 due to the increasing trend of this disease and its rapid progress. Alzheimer's disease

Table 3. Western blot buffer compositions.

Blotting Buffer	Blocking Solution	Antibody Solution
25 mM Tris, pH 7.4, 0.15 M NaCl, 0.1% Tween 20	5% nonfat dry milk in Blotting Buffer, Adjust pH to 7.4	5% nonfat dry milk in Blotting Buffer, Adjust pH to 7.4

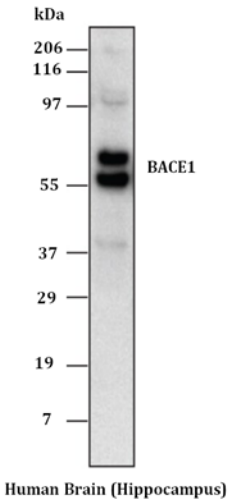

Figure 4. Western blot analysis in *BACE-1* gene.

is caused by the accumulation of beta-amyloid plaques and hyper-phosphorylation of tau protein in the brain (35). According to the Schematic research of Braak and Braak conducted in 1991, dementia caused by amyloid beta (Aβ) has 3 stages and tau phosphorylation has 6 stages. As for the stages of Tao, from the first stage to the second stage, it may take 30 years, but the first to the fifth stage may take 48 years (36). In another study conducted by Swarbrick2019, the role of each miRNA in blood was investigated. This review included the role and relationship of miRNA in blood with inflammation signaling pathways, amyloid beta (Aβ) or tau. The results of this study showed that 44 miRNAs have unknown targets, 14 from amyloid, 10 from inflammation, 7 from apoptosis, 3 from tau, and 13 from other signaling pathways were effective in Alzheimer's disease (35). The results of this research along with other studies on the role of microRNAs show that many groups of microRNAs are effective in Alzheimer's disease mainly through changes in different molecular mechanisms, neurotoxicity, synaptic disorder, phosphorylation, production, storage, or removal of neurotransmitters. As mentioned, MIR107 microRNA 107 causes amyloid precursor protein (APP) breakdown, increases β-site amyloid precursor protein cleaving enzyme (BACE1) expression, and increases the induction of Alzheimer's disease and apoptosis. Other factors affecting Alzheimer's include the following: Fyn: Src family tyrosine kinase / PTPN1: protein tyrosine phosphatase non-receptor type 1 / ITPKB: inositol-trisphosphate 3-kinase B / Sirt1: sirtuin 1 / NSO1: nitric oxide synthase1 / PTEN: phosphatase and tensin homolog / FOXO3: forkhead box O3 / TNFAIP1: TNF alpha-induced protein 1 / BDNF: Brain-derived neurotrophic factor / Rb1: RB transcriptional corepressor 1 / UCHL1: ubiquitin C-terminal hydrolase L1 / RARA: retinoic acid receptor alpha / SNX6: sorting nexin 6 / ROCK1: Rho-associated coiled-coil containing protein kinase 1 / VAMP2: vesicle-associated membrane protein 2 / SPHK1: sphingosine kinase 1 / VAV: vav guanine nucleotide exchange factor 1 / ApoE: apolipoprotein E. Recent research has shown that these factors are related to the immune system, cell cycle, gene expression, cellular response to stress, neuron growth factor signaling, and cellular aging. It is hoped that by relying on cellular and molecular knowledge, the treatment of this disease will be provided.

Conclusion

Reduces miR-107 expression by regulating NF-κB signaling pathway, thereby inhibiting apoptosis in Alzheimer's disease patients. On the other hand, increased expression of miR-107 leads to increased fragmentation of amyloid precursor protein (APP). This factor increases the production of amyloid (Aβ) peptide plaques and increases the expression of the BACE1 gene, ultimately leading to the induction of apoptosis and the induction of Alzheimer's disease.

Conflicts of interests

The authors state no conflicts of interest in this study.

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