Experimed 2024; 14(1): 1-6

REVIEW ARTICLE

DOI: 10.26650/experimed.1395474

Potential Roles of MicroRNAs in Neurodegenerative Diseases

Medinenur Yozlu[1], Duygu Gezen Ak[2], Emrah Yucesan[1]

[1]Department of Neurogenetics, Institute of Neurological Sciences, Istanbul University-Cerrahpasa, Istanbul, Turkiye
[2]Department of Neuroscience, Institute of Neurological Sciences, Istanbul University-Cerrahpasa, Istanbul, Turkiye

ORCID ID: M.Y. 0000-0002-3580-7280; D.G.A. 0000-0001-7611-2111; E.Y. 0000-0003-4512-8764

Cite this article as: Yozlu M, Gezen Ak D, Yucesan E. Potential roles of MicroRNAs in neurodegenerative diseases. Experimed 2024; 14(1): 1-6.

ABSTRACT

Neurodegenerative diseases are defined by advanced neuronal loss and can occur in hereditary or sporadic forms. As is generally known, the most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). Among these, AD is defined by the accumulation of beta-amyloid plaques, hyper phosphorylation of tau proteins, and chronic inflammation leading to neuronal loss. PD is related to the degeneration of dopaminergic neurons in the substantia nigra. Because of the wide heterogeneity of neurodegenerative diseases, various difficulties are encountered in diagnosing disease subtypes and developing effective treatment approaches. In recent years, microRNAs (miRNAs) have become efficient genetic biomarkers for several diseases. miRNAs regulate gene expressions post-transcriptionally and thus play a role in numerous neuronal and non-neuronal cell functions. Prior investigations have indicated the expression of miRNAs to become altered under pathological conditions, thereby suggesting that they may play a role in neurodegenerative diseases. This review focuses on the function of miRNAs in neurodegeneration and the possible contribution of altered levels of miRNAs and their target mRNAs in AD and PD patients compared to the controls shown in the previous studies. In short, altered expressions of miRNAs may play a role as potential diagnostic biomarkers with regard to neurodegenerative diseases.

Keywords: miRNAs, biomarker, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease

INTRODUCTION

Neurodegenerative Diseases

Neurodegenerative diseases are associated with the progressive loss of neurons and are leading causes of death worldwide after cancer and cardiovascular diseases. Many different neurodegenerative diseases occur, but the most prevalent ones are Amyotrophic Lateral Sclerosis, Huntington's disease, Alzheimer's disease (AD), and Parkinson's disease (PD). Diseases occur in hereditary or sporadic forms depending on genetic and environmental factors (1). Although similar features are observed at the cellular level, the most important difference among these diseases is the affected cell and tissue types. For instance, while AD mainly occurs due to neuronal loss in the hippocampus and neocortex, the cells most affected in PD are dopaminergic neurons in the substantia nigra (1, 2). Because of the wide heterogeneity of neurodegenerative diseases, both genetically and clinically, their prevalence also varies (3). About 6.7 million AD patients aged 65 and older were estimated to exist in the USA in 2023; however, approximately 930,000 Americans (≥65 years) had been diagnosed with PD in 2020 (4, 5). In addition, this heterogeneity causes failures in diagnosing and distinguishing among disease subtypes and determining preferentially effective treatment methods. When diagnosing a disease, several different techniques can be applied separately or in combination. In the case of AD, monitoring methods such as positron emission tomography (PET) and magnetic resonance imaging (MRI) can be used, as well as cerebrospinal fluid (CSF) biomarkers such as amyloid beta (Aβ) 42 and phospho-tau. Aβ42 forms plaques and phospho-tau forms neurofibrillary tangles in the brain, contributing to the pathology of AD (6). Meanwhile, α-synuclein in CSF and serum is a biomarker

Corresponding Author: Emrah Yücesan **E-mail:** emrah.yucesan@iuc.edu.tr
Submitted: 24.11.2023 **Revision Requested:** 17.01.2024 **Last Revision Received:** 23.01.2024 **Accepted:** 05.02.2024 **Published Online:** 25.03.2024

for PD. In addition, PET, transcranial sonography (TCS), and dopamine transporter single-photon emission computed tomography (DAT SPECT) techniques can also be used in clinical diagnosis (7, 8).

The biochemical markers and imaging methods mentioned above have variable sensitivities and specificities (9). Moreover, due to the lack of curative treatments for almost all neurodegenerative diseases, the need for early diagnosis and effective therapeutic approaches before disease onset are absolutely present (10). Typically, AD and PD result from pathological instability influencing varied types of neurons at a diverse range of levels. This instability can be identified by alterations in the epigenome (9). MicroRNAs (miRNAs) control gene expression post-transcriptionally and have become a focus in this context (11).

miRNAs and Therapeutic Implementations

miRNAs are small, endogenous non-coding RNA molecules about 21-25 nucleotides in length. The biogenesis of miRNAs starts in the nucleus finishes in the cytoplasm (12). Each miRNA contains an evolutionary conserved region 2-8 nucleotides long called the seed region. The 3′ untranslated region (3′UTR) of the target messenger RNAs (mRNAs) contain complementary sequences to these seed regions, and thus miRNAs control gene expression by degrading mRNAs or inhibiting translation (1). A single miRNA may inhibit the translation of several mRNAs, and numerous miRNAs may control the same mRNA (13). In addition, miRNAs have critical roles in many biological processes, such as apoptosis, proliferation in response to immune stimuli, and differentiation (14–16). Thus, miRNAs' altered levels of expression have been associated with many diseases (1). Examining miRNA expression levels enables one to better understand the molecular pathology of diseases and can be used as potential biomarkers for the early diagnosis of disease. Roughly 70% of miRNAs are produced in the nervous system in humans and are involved in primary signaling pathways (17). Therefore, researchers in recent years have concentrated on examining impaired miRNA expression in brain development and neurodegeneration, with altered expression levels of specific miRNAs having been observed in distinct neurodegenerative diseases, including AD and PD (18).

In addition to the features mentioned above, various studies are present in the literature on miRNAs being used for therapeutic purposes. For instance, decreased expression of miR-125b has been associated with neurotoxic effects in AD, with up-regulated expression of miR-125b by 17ss-estradiol being shown to protect neurons from neurotoxicity (19). In addition, miR-206 has been shown to promote the detrimental effect of Ass42 and to be up-regulated in the temporal cortex of the human brain in AD (20). Donepezil, a miR-206 inhibitor, can relieve the detrimental effects of Ass42 (21). As another example, miRNA's rejuvenation of miR-150 mimics reduced inflammatory cytokines in PD (22). MiR-7 mimics, which are used to recover miR-7 downregulation, have also been shown in MPTP-induced Parkinsonian mice to reduce dopaminergic degeneration and to inhibit microglial activation (23). Another study showed the inhibition of miR-181 in PD to protect against neurodegeneration induced by alpha-synuclein overexpression (24).

As noted above, the positive results obtained from experimental processes conducted with the help of anti-miR have directed researchers towards implementing clinical applications using this approach. As examples, the anti-miR study (ClinicalTrials.gov Identifier: NCT04619420) that is currently in Phase 2 of a clinical trial for treating AD, cognitive dysfunction, and dementia and started on January 6, 2021 is present. That study has reported expectation to finish up on November 5, 2025 and includes 480 individuals. Another clinical study (ClinicalTrials.gov Identifier: NCT05462106) is in Phase 1 and 2 for the treatment of AD. It includes 140 individuals and was initiated on June 21, 2021, with completion planned for June 2026. In addition, a Phase 3 study (ClinicalTrials.gov Identifier: NCT02670083) was conducted between March 22, 2016, and May 31, 2019 with the participation of 813 individuals and aimed to treat AD. All the findings from these studies indicate that future clinical implications will occur regarding anti-miR applications and that more similar studies will be conducted.

miRNAs in Alzheimer's Disease

AD is the most prevalent neurodegenerative disease and is characterized with a loss of neurons, memory loss, and cognitive impairments (25). Patients with AD are seen to express typical features such as personality changes, alterations in emotion, unsuitable social behaviors, and advanced memory impairments (26). Because aging is a significant risk for neurodegenerative diseases, the threat of AD progressing mainly elevates after the age of 65 (27). Ass peptide aggregation and neurofibrillary tangle accumulation due to tau phosphorylation in AD cause amyloidosis, neuronal loss, neuroinflammation, synaptic plasticity, and oxidative stress (28). The etiology of AD remains unclear because of the complexity of the cause and molecular mechanism of the disease; however, accumulation of extracellular Ass peptides and neurofibrillary tangles along with neuroinflammation form the essential biomarkers of AD (26). Because changes in miRNA expression contribute to AD pathogenesis, they could also be used as potential diagnostic biomarkers for the disease (29). In recent years, changes in the expression of many miRNAs have become associated with AD pathogenesis. For instance, miR-9 is a miRNA expressed in the nervous system and related to control of the morphological differentiation of post-mitotic neuronal cells; its level of expression is also seen to change in AD (30). Souza et al. conducted a study in 2020 to investigate the peripheral miR-9-5p expressions of 36 AD patients and 38 healthy controls using quantitative real-time polymerase chain reaction (qRT-PCR). They observed the expression of miR-9-5p in AD patients to have decreased 3-fold in comparison to the controls (31). Similarly, another study conducted by Yılmaz et al. in 2016 with 172 AD patients and 109 healthy controls

demonstrated the AD patients to have an approximately 5-fold decrease in miR-9-5p expression (32). As another example, the miR-29 family of miRNAs are known to post-transcriptionally regulate *BACE1* expression, with the expression of miR-29 being shown to be reduced in AD, resulting in increased *BACE1* expression and increased Ass accumulation (33). A study conducted by Hébert et al. in 2008 evaluated miR-29a and miR-29b-1 expression levels for 11 AD patients with elevated *BACE1* expression levels, 23 AD patients with normal *BACE1* expression levels, and 21 healthy controls using qRT-PCR. Their study showed the expression of miR-29a and -29b-1 to mainly decrease in AD patients, particularly those with elevated *BACE1* expression levels (33). Another miRNA family that suppresses *BACE1* expression is miR-15 (34). The miR-15 family has also been found to have a function in the apoptosis of neurons and tau phosphorylation. As an example of the importance of miR-15, a study conducted by Wu et al. in 2020 included 40 AD patients and 31 healthy controls. Their study examined the expression of 816 blood miRNAs in samples taken from 71 participants and observed essential variations in the expression levels of 71 miRNAs between the AD and control groups. Based on their study's results, they observed a decrease in the miR-15b expression in particular, compared to the controls (35). In addition to down-regulated miRNAs, other miRNAs are found to be upregulated in AD. Examples of the upregulated miRNAs can be given as miR-195, miR-106b-3p, and miR-34a (26). A study performed by Zang et al. in 2021 included 117 AD patients and 106 healthy controls; their study also evaluated the serum miR-128 level using qRT-PCR and found miR-128 expression to have significantly increased (36). Another study showed miR-128 to downregulate the expression of *PPAR-γ* and to intensify the Aβ-induced damage survival of neurons in AD (37). Thus, upregulated miR-128 can have a remarkable function in AD's progression. When taking the aforementioned into account, miRNAs obviously have essential roles in both the etiopathogenesis of AD and possess significant potential as genetic biomarkers. These details will be specified below through the similar features that are seen in PD.

miRNAs in Parkinson's Disease

PD is the second most common neurodegenerative disease associated with the advanced loss of neurons in the brain, especially dopaminergic neurons in the substantia nigra. Degeneration of these neurons in PD patients may result in impaired motor function and clinical signs such as rigidity, postural instability, resting tremor, and bradykinesia, which are associated with a reduction in dopaminergic neurons (38). PD onset occurs generally after the age of 60 years and includes the interaction of genetic and elevated-risk environmental factors such as the consumption of dairy products, pesticides, traumatic brain injury, and a history of melanoma (39). PD involves the accumulation of α-synuclein in the Lewy bodies, which then impairs various pathways and activates neuroinflammation (40). Motor dysfunction begins to develop after approximately 70% of the dopaminergic neurons in the substantia nigra have degenerated. This early phase of PD takes 8-17 years and involves complex mechanisms. Thus, the presence of preclinical biomarkers for PD is essential to the development of future neuroprotective approaches (41). Several specific miRNAs have been shown many times in the literature to have a function in the pathogenesis of PD. For example, Wu et al. in 2022 investigated *SNCA*-associated miRNA expressions in 75 PD patients and 73 healthy controls using qRT-PCR and found miR-153 and miR-223 expression levels to have decreased mainly in the PD patients compared to the controls (42). In 2020, Li et al. showed miR-150 to be another down-regulated miRNA in PD pathogenesis. They evaluated neuroinflammation-associated miR-150 expression in 80 PD patients and 60 healthy controls and ascertained miR-150 expression to have decreased in the PD patients when compared to the controls (22). In addition, the literature has shown up-regulated miRNA expression to occur in PD pathogenesis. For instance, miR-132 is an miRNA that has been negatively correlated with its downstream molecule nuclear receptor *NURR1* (also known as *NR4A2*), which is one of the main factors that sustain dopaminergic features. Yang et al. conducted a study in 2019 involving 667 people (269 sporadic PD patients, 222 healthy controls, and 176 individuals with several non-PD neurodegenerative diseases). They evaluated the expression levels of miR-132 and *NURR1* and indicated miR-132 expression levels to be elevated in PD patients when compared to the healthy and non-PD controls. *NURR1* was also crucially reduced in the PD patients compared to the healthy and non-PD controls, thus showing a negative correlation between reduced levels of *NURR1* expression and increased levels of miR-132 expression in PD (43). As mentioned above, the miR-29 family has decreased levels in AD pathogenesis. In addition, these miRNAs (miR-29a, -29b, and -29c) have been related to cognitive impairment in PD, with Han et al. assessing miR-29 expression levels in 98 PD patients and 40 healthy controls to examine this. They classified patients into three groups: PD patients with usual conditions (n = 39), PD patients with dementia (n = 22), and PD patients with mild cognitive impairment (n = 37) and found all miRNAs to be down-regulated in all three groups of patients compared to the healthy control group. In addition, they found the miR-29 expression levels in the PD patients with dementia to be lower than that for PD patients with normal conditions, thus relating the decreasing trend of these miRNAs to more severe PD (44). When considering the roles miRNAs play in physiological and pathological conditions alongside the alteration of their expression in diseases, miRNAs have the potential to serve as biomarkers for the early diagnosis and prognosis of disease and also as targets for therapeutic intervention.

CONCLUSION

As explained with the examples above, miRNAs play important roles in many physiological conditions, with miRNA de-regulation having been able to be associated with many pathological states. Obviously, miRNAs also have a function in the molecular etiopathogenesis of neurodegenerative diseases. This role may involve up-regulation or down-regulation, as is the case in AD and PD, the two most common

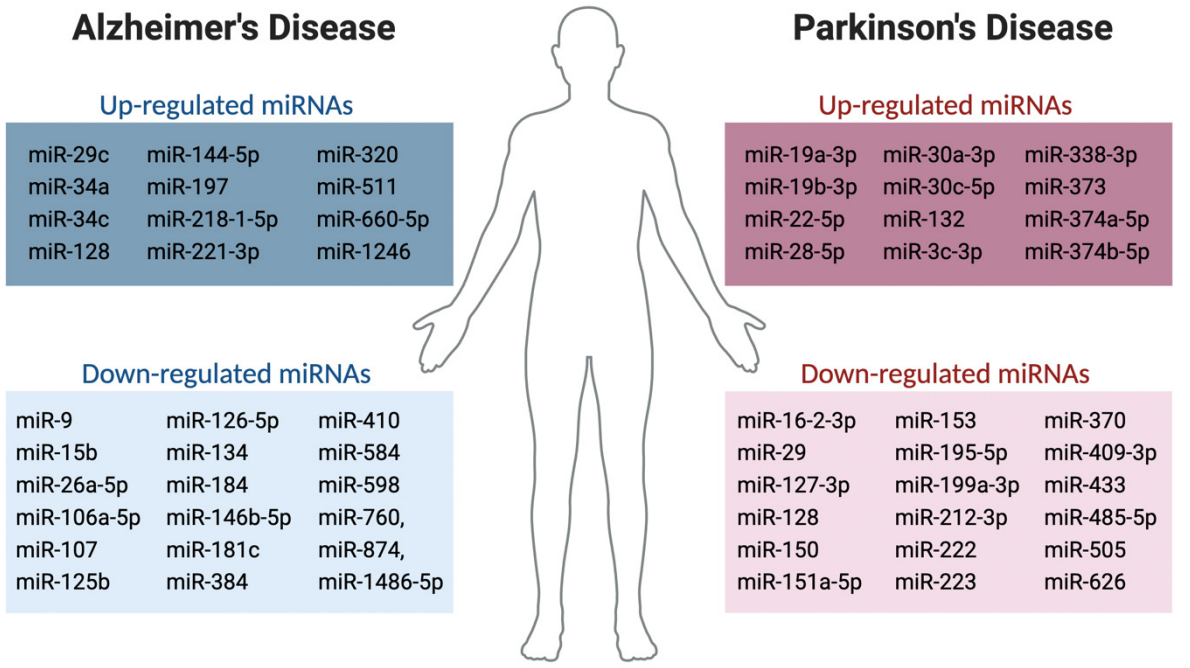

Figure 1. miRNAs alterations in Alzheimer's and Parkinson's diseases.

neurodegenerative diseases exemplified in this review. Figure 1 shows several upregulated and downregulated miRNAs in AD and PD (32, 33, 35, 45–48). The number of studies evaluating miRNAs will undoubtedly increase in the future, and several reasons are thought to exist for this. First of all, significance in demonstrating the roles miRNAs have regarding the clarification of the mechanisms and progression of neurodegenerative diseases. Another reason is the potential miRNAs have as genetic biomarkers. The most important aspect of this is that many studies have shown miRNAs to be able to be utilized in the early diagnosis and follow-up of the disease. Lastly, attempts have been made to develop various therapeutic approaches utilizing the regulatory functions of miRNAs, especially in recent years. Anti-miR oligonucleotides, antagomirs, locked nucleic acid anti-miRs, and miR masks that are used to suppress miRNAs, as well as miRNA expression vectors and miRNA mimics that are used to restore miRNA expression reveal other aspects of the importance these small non-coding molecules have (1).

This article has compiled up-to-date information on the subject of the functions miRNAs have in neurodegeneration by evaluating the case of AD and PD. As mentioned above, this study assumes that studies in this field will gain more importance and increase in number in the future.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- E.Y., M.Y., D.G.A.; Data Acquisition- E.Y., M.Y.; Data Analysis/Interpretation- E.Y., M.Y., D.G.A.; Drafting Manuscript- M.Y.; Critical Revision of Manuscript- E.Y., D.G.A.; Final Approval and Accountability- E.Y., M.Y., D.G.A.

Conflict of Interest: The authors declare that they have no competing interests.

Financial Disclosure: The authors declare that this study has received no financial support.

REFERENCES

1. Roy B, Lee E, Li T, Rampersaud M. Role of miRNAs in neurodegeneration: from disease cause to tools of biomarker discovery and therapeutics. Genes (Basel) 2022; 13(3): 425.
2. Scheff SW, Price DA. Alzheimer's disease-related alterations in synaptic density: neocortex and hippocampus. J Alzheimers Dis 2006; 9(3 Suppl): 101-15.
3. Ringman JM, Goate A, Masters CL, Cairns NJ, Danek A, Graff-Radford N, et al. Genetic heterogeneity in alzheimer disease and implications for treatment strategies. Curr Neurol Neurosci Rep 2014; 14(11): 499.
4. 2022 Alzheimer's disease facts and figures. Alzheimers Dement 2022; 18(4): 700–89.
5. Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW, et al. Prevalence of Parkinson's disease across North America. NPJ Parkinson's Disease 2018; 4(1): 1–7.
6. Ausó E, Gómez-Vicente V, Esquiva G. Biomarkers for Alzheimer's disease early diagnosis. J Pers Med 2020; 10(3): 1–27.
7. Zubelzu M, Morera-Herreras T, Irastorza G, Gómez-Esteban JC, Murueta-Goyena A. Plasma and serum alpha-synuclein as a biomarker in Parkinson's disease: a meta-analysis. Parkinsonism Relat Disord 2022; 99: 107–15.

8. Suwijn SR, van Boheemen CJM, de Haan RJ, Tissingh G, Booij J, de Bie RMA. The diagnostic accuracy of dopamine transporter SPECT imaging to detect nigrostriatal cell loss in patients with Parkinson's disease or clinically uncertain parkinsonism: a systematic review. EJNMMI Res 2015; 5(1): 12.
9. Mayo S, Benito-León J, Peña-Bautista C, Baquero M, Cháfer-Pericás C. Recent evidence in epigenomics and proteomics biomarkers for early and minimally invasive diagnosis of Alzheimer's and Parkinson's diseases. Curr Neuropharmacol 2021; 19(8): 1273–303.
10. Manna I, de Benedittis S, Quattrone A, Maisano D, Iaccino E, Quattrone A. Exosomal miRNAs as potential diagnostic biomarkers in Alzheimer's disease. Pharmaceuticals (Basel) 2020; 13(9): 1–16.
11. Viswambharan V, Thanseem I, Vasu MM, Poovathinal SA, Anitha A. miRNAs as biomarkers of neurodegenerative disorders. Biomark Med 2017; 11(2): 151–67.
12. Idda ML, Munk R, Abdelmohsen K, Gorospe M. Noncoding RNAs in Alzheimer's disease. Wiley Interdiscip Rev RNA 2018; 9(2): 10.1002/wrna.1463.
13. Anglicheau D, Muthukumar T, Suthanthiran M. MicroRNAs: small RNAs with big effects. Transplantation 2010; 90(2): 105–12.
14. Bueno MJ, De Castro IP, Malumbres M. Control of cell proliferation pathways by microRNAs. Cell Cycle 2008; 7(20): 3143–8.
15. Su Z, Yang Z, Xu Y, Chen Y, Yu Q. MicroRNAs in apoptosis, autophagy and necroptosis. Oncotarget 2015; 6(11): 8474–90.
16. Leung AKL, Sharp PA. MicroRNA functions in stress responses. Mol Cell 2010; 40(2): 205–15.
17. Nowak JS, Michlewski G. miRNAs in development and pathogenesis of the nervous system. Biochem Soc Trans 2013; 41(4): 815–20.
18. Bushati N, Cohen SM. MicroRNAs in neurodegeneration. Curr Opin Neurobiol 2008; 18(3): 292–6.
19. Micheli F, Palermo R, Talora C, Ferretti E, Vacca A, Napolitano M. Regulation of proapoptotic proteins Bak1 and p53 by miR-125b in an experimental model of Alzheimer's disease: Protective role of 17β-estradiol. Neurosci Lett 2016; 629: 234–40.
20. Lee ST, Chu K, Jung KH, Kim JH, Huh JY, Yoon H, et al. miR-206 regulates brain-derived neurotrophic factor in Alzheimer disease model. Ann Neurol 2012; 72(2): 269–77.
21. Wang CN, Wang YJ, Wang H, Song L, Chen Y, Wang JL, et al. The anti-dementia effects of donepezil involve miR-206-3p in the hippocampus and cortex. Biol Pharm Bull 2017; 40(4): 465–72.
22. Li H, Yu L, Li M, Chen X, Tian Q, Jiang Y, et al. MicroRNA-150 serves as a diagnostic biomarker and is involved in the inflammatory pathogenesis of Parkinson's disease. Mol Genet Genomic Med 2020; 8(4): e1189.
23. Zhou Y, Lu M, Du RH, Qiao C, Jiang CY, Zhang KZ, et al. MicroRNA-7 targets nod-like receptor protein 3 inflammasome to modulate neuroinflammation in the pathogenesis of Parkinson's disease. Mol Neurodegener 2016; 11(1): 28.
24. Stein CS, McLendon JM, Witmer NH, Boudreau RL. Modulation of miR-181 influences dopaminergic neuronal degeneration in a mouse model of Parkinson's disease. Mol Ther Nucleic Acids 2022; 28: 1–15.
25. Vahia VN. Diagnostic and statistical manual of mental disorders 5: a quick glance. Indian J Psychiatry 2013; 55(3): 220.
26. Zhao Y, Zhang Y, Zhang L, Dong Y, Ji H, Shen L. The potential markers of circulating microRNAs and long non-coding RNAs in Alzheimer's disease. Aging Dis 2019; 10(6): 1293–301.
27. Hickman RA, Faustin A, Wisniewski T. Alzheimer Disease and its growing epidemic: risk factors, biomarkers, and the urgent need for therapeutics. Neurol Clin 2016; 34(4): 941–53.
28. Calabrò M, Rinaldi C, Santoro G, Crisafulli C. The biological pathways of Alzheimer disease: a review. AIMS Neurosci 2020; 8(1): 86–132.
29. Zhao Y, Jaber V, Alexandrov PN, Vergallo A, Lista S, Hampel H, et al. microRNA-based biomarkers in Alzheimer's disease (AD). Front Neurosci 2020; 14: 585432.
30. Yuva-Aydemir Y, Simkin A, Gascon E, Gao FB. MicroRNA-9: functional evolution of a conserved small regulatory RNA. RNA Biol 2011; 8(4): 557–64.
31. Souza VC, Morais GS, Henriques AD, Machado-Silva W, Perez DIV, Brito CJ, et al. Whole-blood levels of microRNA-9 are decreased in patients with late-onset Alzheimer Disease. Am J Alzheimers Dis Other Demen 2020; 35: 1533317520911573.
32. Yllmaz ŞG, Erdal ME, Özge AA, Sungur MA. Can peripheral microRNA expression data serve as epigenomic (upstream) biomarkers of Alzheimer's disease? OMICS 2016; 20(8): 456–61.
33. Hébert SS, Horré K, Nicolaï L, Papadopoulou AS, Mandemakers W, Silahtaroglu AN, et al. Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. Proc Natl Acad Sci USA 2008; 105(17): 6415–20.
34. Gong G, An F, Wang Y, Bian M, Yu LJ, Wei C. miR-15b represses BACE1 expression in sporadic Alzheimer's disease. Oncotarget 2017; 8(53): 91551–7.
35. Wu HZY, Thalamuthu A, Cheng L, Fowler C, Masters CL, Sachdev P, et al. Differential blood miRNA expression in brain amyloid imaging-defined Alzheimer's disease and controls. Alzheimers Res Ther 2020; 12(1): 59.
36. Zhang M, Han W, Xu Y, Li D, Xue Q. Serum miR-128 serves as a potential diagnostic biomarker for Alzheimer's disease. Neuropsychiatr Dis Treat 2021; 17: 269–75.
37. Geng L, Zhang T, Liu W, Chen Y. Inhibition of miR-128 abates Aβ-mediated cytotoxicity by targeting PPAR-γ via NF-κB inactivation in primary mouse cortical neurons and Neuro2a cells. Yonsei Med J 2018; 59(9): 1096–106.
38. Balestrino R, Schapira AHV. Parkinson disease. Eur J Neurol 2020; 27(1): 27–42.
39. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. Lancet Neurol 2016; 15(12): 1257–72.
40. Hallett PJ, Engelender S, Isacson O. Lipid and immune abnormalities causing age-dependent neurodegeneration and Parkinson's disease. J Neuroinflammation 2019; 16(1):153
41. Cacabelos R. Parkinson's disease: from pathogenesis to pharmacogenomics. Int J Mol Sci 2017; 18(3): 551.
42. Wu L, Xu Q, Zhou M, Chen Y, Jiang C, Jiang Y, et al. Plasma miR-153 and miR-223 levels as potential biomarkers in Parkinson's disease. Front Neurosci 2022; 16: 865139.
43. Yang Z, Li T, Li S, Wei M, Qi H, Shen B, et al. Altered expression levels of microRNA-132 and Nurr1 in peripheral blood of Parkinson's disease: potential disease biomarkers. ACS Chem Neurosci 2019; 10(5): 2243–9.
44. Han L, Tang Y, Bai X, Liang X, Fan Y, Shen Y, et al. Association of the serum microRNA-29 family with cognitive impairment in Parkinson's disease. Aging 2020; 12(13): 13518–28.

45. Guo R, Fan G, Zhang J, Wu C, Du Y, Ye H, et al. A 9-microRNA signature in serum serves as a noninvasive biomarker in early diagnosis of Alzheimer's disease. J Alzheimer's Dis 2017; 60(4): 1365–77.
46. Burgos K, Malenica I, Metpally R, Courtright A, Rakela B, Beach T, et al. Profiles of extracellular miRNA in cerebrospinal fluid and serum from patients with Alzheimer's and Parkinson's diseases correlate with disease status and features of pathology. PLoS One 2014; 9(5): e94839.
47. Khoo SK, Petillo D, Kang UJ, Resau JH, Berryhill B, Linder J, et al. Plasma-based circulating microRNA biomarkers for Parkinson's disease. J Parkinsons Dis 2012; 2(4): 321–31.
48. He S, Huang L, Shao C, Nie T, Xia L, Cui B, et al. Several miRNAs derived from serum extracellular vesicles are potential biomarkers for early diagnosis and progression of Parkinson's disease. Transl Neurodegener 2021; 10(1): 1–12.