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REVIEW ARTICLE

miRNAs Expressions and Interaction with Biological Systems in Patients with Alzheimer`s Disease. Using miRNAs as a Diagnosis and Prognosis Biomarker

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SUMMARY

Background: **A high percentage of patients develop Alzheimer`s disease (AD). The main signs are loss of memory and cognitive functions which have a significant impact on lifestyle. Numerous studies have been conducted to identify new biomarkers for early diagnosis of patients with AD. An ideal biomarker is represented by the expression of miRNAs. In this paper, we want to summarize expressions miRNAs in AD. We also want to present the pathophysiological and genetic interactions of miRNAs with protein systems in these patients.**
Methods: **For the study, we examined available studies in scientific databases, such as PubMed and Scopus. The studies were searched using the keywords "miRNAs expression", "Alzheimer`s disease", "genetic polymorphisms", and "genetic biomarkers".**
Results: **For the assessment and monitoring of patients with AD, the expression of miRNAs can be used successfully due to increased specificity and selectivity. Moreover, the expression of miRNAs can provide important answers regarding possible genetic interactions and genetic therapeutic regimens.**
Conclusions: **For the evaluation and non-invasive monitoring of patients with Alzheimer`s disease the expression of miRNAs can be successfully used.**
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KEY WORDS

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INTRODUCTION

Worldwide a high percentage of patients develop Alzheimer`s disease (AD). From a pathophysiological point of view, AD is a progressive neurodegenerative disease characterized by severe dysfunction of cognitive functions and memory [1,2]. Immobility and death can also occur in patients with severe dysfunctions [3]. At this point, the etiology and pathophysiological mechanisms

of AD have not been elucidated yet. Recent studies have shown that neural cells are attacked by amyloid β-protein peptides and Tau proteins, leading to their death [4-6]. Recent studies have used the expression of these proteins as a method of assessment and early diagnosis of patients with AD. Unfortunately, up to now the provided methods do not have high specificity and accuracy for the diagnosis of these patients. A marker of interest that could become the future marker for evaluating patients with AD is the expression of miRNAs [7-9]. In this updated paper, we want to summarize the most specific miRNA expressions involved in the pathophysiology of AD. Moreover, we want to bring up a high panel of miRNA expressions that can be used for early assessment and continuous monitoring of patients with AD.

Pathophysiological aspects for Alzheimer`s disease (AD)

From a pathophysiological point of view two main mechanisms define AD, which are represented by amyloid plaques and neurofibrillary tangles. From a biochemical point of view, amyloid plaques are represented by extraneuronal deposits of amyloid β-protein (Aß). On the other hand, neurofibrillary tangles consist of intraneuronal filaments containing microtubule-associated protein tau [4,5,10]. Recent studies have revealed the presence of increased amounts of Tau, a 50 - 70 kDa microtubule-associated protein mainly in axons (Figure 1) [11].

Numerous studies have shown that apolipoprotein E (APOE) is a high genetic risk factor for developing AD. In the mechanisms involved in the development of AD, APOE ε4 allele is a risk factor and ε2 allele a protective factor [1,12]. From a biochemical point of view, APOE has three isomeric forms of clinical importance, represented by APOE2, APOE3, and APOE4. They are produced mainly by astrocytes and microglia. It is known that there is a strong link between amyloid β accumulation and APOE [1,12-14].

It has also been identified that brain-derived neurotrophic factor (BDNF) is responsible for protecting neural cells from the neurotoxic actions of Aβ peptide. Ferrer et al., showed that BDN is low in the frontal cortex and hippocampus in patients with AD [15]. Recently, a number of interactions of miRNAs species with different biochemical systems involved in the pathophysiology of AD have been reported, such as amyloid precursor protein (APP), Tau or β-site amyloid precursor protein cleaning enzyme-1 (BACE1) [16-18]. Other studies showed significant changes in the expression of miRNAs in patients with AD compared with healthy ones. Thus, their use as diagnostic and prognostic tools came to the attention of researchers worldwide.

miRNA production biochemical mechanisms

The start regarding miRNA biogenesis and biosynthesis occurs in the cell nucleus [19-21]. Synthesis of miRNAs starts through the action of RNA polymerase II on specific genes found in the nucleus. Following the reactions that occur, the first species produced are called pri-miRNAs. RNA polymerase III endonuclease (Drosha), and DiGeorge Syndrome Critical Region 8 (DGCR8) act on pri-miRNAs, forming pre-miRNAs [22,23]. Pre-miRNAs are transported into the cytoplasm by coupling carrier protein exportin 5. Subsequently the attack of RNAse III endonuclease (Dicer) and TAR RNA binding protein (TRBP) form double-stranded miRNA species. Mature species are engaged in RNA induced silencing complex (RISC) and exported from the cell in various forms (Figure 2) [24].

Because miRNAs shows high specificity and selectivity for certain types of fluids and tissues they are considered non-invasive biomarkers ideal for detecting a wide range of pathophysiologies [25-27]. Weber et al. identified 714 microRNAs in 12 types of biological fluids such as blood, plasma, urine, cerebrospinal fluid, saliva or semen [28]. The most common methods for analyzing miRNA species are quantitative real-time PCR (qPCR) and digital droplet PCR (ddPCR) [29-31].

Expression of miRNAs in Alzheimer`s disease (AD)

Currently, classic diagnostic methods for AD are represented by the assessment of your total (t-tau), amyloid-β42 (Aβ42), and phosphorylated tau (p-tau) from the cerebrospinal fluid. However, they exhibit low specificity and selectivity for this pathology. An adequate biomarker for assessing and monitoring the evolution of AD is the expression of miRNAs. There have been various studies made on the expression of miRNAs in various biological fluids. Regarding the analyses of genetic species from the blood of patients with AD, Geekiyanage et al., found a significant decrease in the concentration of miRNA-137, miRNA-181c, miRNA-9, and miRNA-29 [32]. A similar study was conducted by Tan et al., who reported an altered expression for miRNA-342-3p in patients with AD. Moreover, they found a sensitivity of 81.5% and a specificity of 70.1% in terms of detection of pathophysiological changes in AD [33]. Another biological fluid of interest in evaluating miRNA expressions in patients with AD is cerebrospinal fluid. Cogswell et al., identified 60 species of miRNA that present different expressions in patients with AD. Among these the most significant changes are the overexpression for miRNA-27a, miRNA-27b, miRNA-34a, miRNA-100, miRNA-125b, miRNA-381, miRNA-422, miRNA-26a, miRNA-422a, miRNA-423, miRNA-92, miRNA-145, miRNA-148a and downregulation for miRNA-9, miRNA-98, miRNA-132, miRNA-30c, miRNA-26a, miRNA-200c, miRNA-210, miRNA-146b, miRNA-212, and miRNA-425 [34]. Muller et al., found a decrease for miRNA-146a in patients with AD. They also showed a strong correlation between low concentration for miRNA-146a and poor prognosis of this pathology [35]. A similar study made by Nunez-Iglesias et al., highlights abnormal changes for miRNA-18b, miRNA-34c , miRNA-629, miRNA-637, miRNA-657, miRNA-615, miRNA-661, miRNA-15903, miRNA-

44691, miRNA-09369, miRNA-221, miRNA-216, miRNA-325, miRNA-506, miRNA-612, miRNA-515-3p, miRNA-768-3p, miRNA-06164, miRNA-45496, and miRNA-32339 [36]. Another system involved in various pathological mechanisms of AD development is ubiquitin carboxy-terminal hydrolase L1 (UCHL1). Numerous studies have reported a decrease in concentration of UCHL1 soluble in patients with AD. Also highlighted were important links between the activity of UCHL1 and miRNAs expression. Zhao et al., identified that miRNA-922 is responsible for lowering the concentration UCHL1. Moreover, they have shown that miRNA-922 is responsible for increasing levels of p-tau by modulating UCHL1, thereby developing AD [37]. A similar study was conducted by Wang et al., who reported significant implications of miRNA-107 regarding the modulation mechanisms of the 3`-untranslated region (UTR) of the β-site amyloid precursor protein-cleaning enzyme 1 (BACE1) responsible for precipitating AD [38]. Banzhaf-Strathmann et al., studied the biochemical implications of miRNA-125b in the pathophysiological process of the development of AD. In the study, they showed that the increase in miRNA-125b is involved in the hyperphosphorylation of the activity of p53, cdk5, and p44/42-MAPK signaling. Moreover, they reported that miRNA-125b is responsible for the tau phosphorylation leading to worsening of AD [39]. Long et al., in a similar study reported significant implications in terms of modulating BACE1 by miRNA-339-5p. Following this study they showed that by activating BACE1 through miRNA-339-5p, it can become a successful therapeutic target in patients with AD [40]. Several studies have also reported a number of other protein systems involved in modulating AD. Among these we can find phosphatase and tensin homolog (PTEN), E1A binding protein p300 (P300), and forkhead box O3a (FOXO3a) [41,42]. Wong et al., investigated the expression of these proteins as well as the interactions with miRNAs in AD. In the study, they showed that miRNA-132 and miRNA-212 are in close correlation with FOXO3a and PTEN signaling pathways. Moreover, it was shown that these systems are responsible for accelerating the neurodegenerative mechanisms in AD [41]. Barak et al., conducted a study regarding the expression of miRNAs in AD, reporting significant changes in terms of the concentration of miRNA-325 [43]. A similar study conducted by Ghanbari et al., reported changes for the expression of miRNA-1229-3p [44]. Dong et al., also reported a decrease in the concentration of miRNA-31, miRNA-93, miRNA-143, and miRNA-146a in patients with AD [45]. Denk et al., report significant changes with an accuracy of 95.5% for miRNA-100, miRNA-103, and miRNA-375 in the cerebrospinal fluid of patients with AD. A similar study conducted by Kumar et al., highlights relevant changes for let-7d-5p, miRNA-191-5p, miRNA-301a-3p, and miRNA-545-3p in plasma of patients with AD [46]. Also, Lai et al., reported aberrant changes in the expression of miRNA-34a, miRNA-449a, miRNA-564, miRNA-432, miRNA-548d, miRNA-572, and miRNA-652 in neurodegenerative pathologies of AD [47]. Leidinger et al., reported changes for let-77-5p, miRNA-1285-5p, miRNA-107, miRNA-103a-3p, miRNA-26b-5p, miRNA-532-5p, miRNA-151a-3p, miRNA-161, miRNA-112, miRNA-510-3p, and let-7d-3p in patients with AD [48]. Delay et al., studied a series of genetic polymorphisms in AD. Following the study, they showed significantly altered expression for the rs9909-c allele in the 3`-UTR of NUP160. Significant growth was also reported for miRNA-1185-1-3p for the rs9909 G-allele [49]. Muller et al., identified a of growth for miRNA-29a expression in the cerebrospinal fluid in patients with AD [50]. Sørensen et al., analyzed the expression of miRNAs in the cerebrospinal fluid in patients with AD. In the study they showed an increase in expression of let-7i-5p and miRNA-15-5p and a decrease in the expression of miRNA-29c-3p in AD patients compared to healthy controls. Regarding the expression of miRNAs in the blood, an increase for miRNA-590-5p and miRNA-142-5p and a decrease for miRNA-194-5p were reported [51]. A similar study was performed by Villela et al., which showed an increase in expression of miRNA-9-1 miRNA-9-3 miRNA-181c, miRNA-124-1, miRNA-146b, and miRNA-451 [52]. Hara et al., reported a downregulation for miRNA-501-3p, let-77-5p, and miRNA-26b-5p. Moreover, they highlighted a number of statistical correlations between the expression of miRNA-501-3p and a series of specific biochemical mechanisms specific for the augmentation of neurodegenerative status in patients with AD [53]. Li et al., studied the expression of miRNA-613 in patients with AD, using cerebrospinal fluid as the biological fluid. The study revealed a significant decrease for miRNA-613 in patients with AD. They also correlated this significant decrease with a drastic decrease for the expression of BDNF [3].

Regarding the expression of miRNAs in brain mass, Wang et al., conducted a study regarding miRNA changes in human cerebral cortical gray matter and white matter.

Following the study, they highlighted significant increases for the miRNA expressions in grey matter as follows, miRNA-518e, miRNA-574-5p, miRNA-498, miRNA-518a-5p, miRNA-525-5p, miRNA-300, mi RNA-576-3p, miRNA-583, miRNA-146b-3p, miRNA-490-3p, miRNA-549, miRNA-516a-5p, miRNA-510, miRNA-184, miRNA-516b, miRNA-298, miRNA-214, miRNA-198, miRNA-451, miRNA-144, miRNA-424, let-7e and increases of the expressions of miRNAs in white matter, such as miRNA-509-5p, miRNA-574-3p, miRNA-576-5p, and miRNA-302e. Regarding the downregulation of miRNA expressions in cerebral mass, following the study, they reported a significant decrease in grey matter for miRNA-485-3p, miRNA-381, miRNA-124, miRNA-34a, miRNA-129-5p, miRNA-29a, miRNA-143, miRNA-136, miRNA-145, miRNA-138, miRNA-129-3p, miRNA-128, miRNA-379, miRNA-299-5p, miRNA-218, miRNA-149,

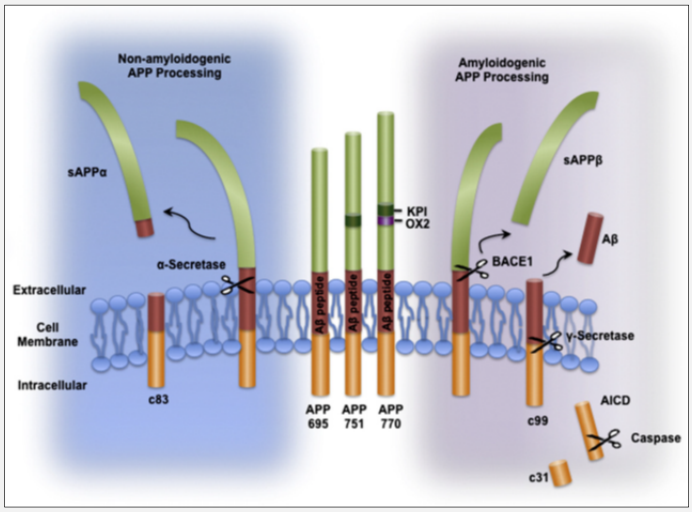

Figure 1. Schematic drawing of the Amyloid Precursor Protein (APP) and its processing pathways.

In humans, APP exists in three major isoforms that are generated by alternative splicing and differ mainly by the presence or absence of the Kunitz-type protease inhibitor (KPI) and OX2 homology domains. APP can be processed by α-secretase in a nonamyloidogenic pathway, which precludes the formation of Aβ and generates soluble APPα (sAPPα) and a C-terminal fragment (c83). Alternatively, in the amyloidogenic pathway, cleavage by the β-secretase BACE1 generates soluble APPβ (sAPPβ), which is secreted, and a C-terminal fragment (β-CTF or c99). Subsequent cleavage of c99 by the γ-secretase complex generates Aβ and the APP intracellular domain (AICD) which can be further cleaved by caspases to produce a c31 fragment. The figure was reproduced from Schonrock N et al. [54], with Elsevier permission.

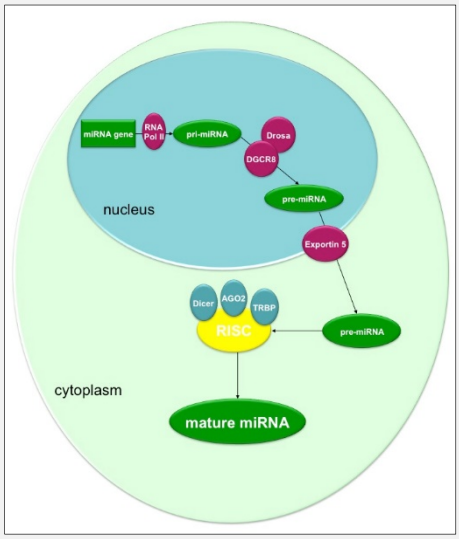

Figure 2. Biogenesis mechanism for microRNAs (miRNAs).

The synthesis of microRNAs begins in the nucleus with the action of RNA polymerase II on protein-coding. This forms a first species, called pri-microRNA. Through successive reactions of poly-adenylation catalyzed by DGCR8 and Drosa the precursor for the microRNAs species is obtained, called pre-microRNA. pre-microRNA thus formed is transported into the cytoplasm through exportin 5. In the cytoplasm the Dicer complex acts on the pre-microRNA, TRBP and AGO2, forming double-stranded mature microRNA (19-24 nucleotides). The figure was reproduced from Schonrock N et al. [24].

miRNA-135a, miRNA-7, miRNA-127-5p, miRNA-127-3p, miRNA-491-5p, miRNA-376c, miRNA-377, miRNA-95, miRNA-222, miRNA-29b, miRNA-329, miRNA-495, miRNA-551b, miRNA-195, miRNA-125b, miRNA-30b, miRNA-221, miRNA-139-5p, miRNA-487a, miRNA-487b, miRNA-107, miRNA-146b-5p, miRNA-29c, miRNA-30a, miRNA-582-5p, miRNA-103, miRNA-342-3p, miRNA-331-3p, miRNA-30c, miRNA-30d, miRNA-382, miRNA-22, miRNA-125a-5p, miRNA-491-3p, miRNA-423-5p, miRNA-34b, miRNA-422a, miRNA-34c-5p, miRNA-584, miRNA-219-5p, miRNA-338-3p, miRNA-219-2-3p, miRNA-338-5p, miRNA-181a, miRNA-181b, let-7b, miRNA-151-3p, miRNA-197, miRNA-19a, miRNA-20a, miRNA-17, miRNA-106a, miRNA-32, miRNA-340, miRNA-19b, miRNA-21, miRNA-151-5p, miRNA-194, let-7c, miRNA-330-3p, and miRNA-27b. Also they showed a decrease for miRNA-425, miRNA-191, miRNA-519d, let-7g, miRNA-98, miRNA-99a, and miRNA-30e for gray matter [38].

CONCLUSION

miRNAs are involved in several pathophysiological mechanisms responsible for the generation and augmentation of AD. Thus, the expression of miRNAs becomes a tool for diagnosis and continuous monitoring especially for patients with AD. Moreover, by blocking some specific miRNA mechanisms, the pathophysiological effects responsible for worsening clinical status of these patients can be reduced. miRNAs thus become both an important genetic marker, as well as a factor for the future treatment of patients with AD. However, numerous studies are necessary to develop a significant panel of miRNA expressions that can be used as a marker for screening and diagnostic purposes.

Declaration of Interest:
Nothing to declare.

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