

Alzheim(i)R: MicroRNAs in Alzheimer's Disease

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Editorial

Alzheimer's Disease (AD) is a progressive degenerative disease affecting the central nervous system, characterized by early memory impairments followed by cognitive deficit as aphasia, agnosia and apraxia. AD affects over 35 million individuals worldwide and is expected to affect 115 million by 2050 [1]. Cellular and molecular neurodegeneration detected in AD is characterized by synapse and neuronal loss, extracellular amyloid β ($A\beta$) peptide accumulation and intracellular neurofibrillary tangles (hyperphosphorylated tau) [2,3]. Less than 1% of AD cases are familial, (onset before 60 to 65 years of age) due to mutations in three genes, APP, presenilin 1 (PSEN1), and presenilin 2 (PSEN2), all involved in Abeta overproduction [4]. To date, high Ab levels were suggested to trigger neuronal dysfunctions as major contributors to disease development in the familial form of AD, but for the majority of AD cases, also called sporadic AD, with no obvious genetic bases, other mechanisms are expected to be responsible.

Recently, expression profiles of microRNA (miRNA) in Alzheimer's disease brain revealed alterations in many individual miRNAs, and several in vitro and in vivo studies have suggested that a deregulated microRNA expression could contribute to AD [5,6].

MicroRNAs are small 20-22-nucleotides, double stranded non-coding RNAs, that modulate gene expression at the post-transcriptional level [7]. One strand of an miRNA is incorporated into the Argonaute-containing RNA-induced silencing complex (RISC) and drives the RISC to bind target mRNAs, leading to translational repression and/or mRNA destabilization. The target mRNAs are recognized depending on the complementarities between positions 2 to 8 from the 5' of miRNA (the seed sequence), and an miRNA Responsive Element (MRE) usually located within the mRNA 3' untranslated region (3' UTR) [7]. In mammals the interaction between miRNAs and MREs generally results in either the block of translation or the decay of the target mRNAs, which are deadenylated, decapped and eventually degraded [8]. MiRNAs are abundantly expressed in the brain, where they have been found to play important roles in the regulation of brain function and neurological disorders [9-12]. It is noteworthy that neurons compartmentalize specific mRNAs in different subcellular compartments, and miRNAs may provide a unique system to spatially regulate gene expression [13]. The miRNAs can modulate the expression of multiple mRNA targets, and are candidates for temporally and spatially regulating several context-dependent functions in neurons, ranging from early neurogenesis and neuronal differentiation to dendritic morphogenesis and synaptic plasticity, from memory and behaviour to cognition in the brain. Therefore, diverse miRNA repertoires in the brain likely contribute to the dissimilarities between human and chimpanzee, arguing for a role of miRNA in brain evolution and function [14,15].

Are miRNAs involved in the post-transcriptional regulation of associated gene in AD pathogenesis? Could miRNAs have a pivotal role in intricate pathogenetic networks of AD? Are miRNAs useful biomarkers of AD? Could miRNAs be considered as potential molecular target in the AD?

MicroRNAs have been identified as regulators of key genes involved in Alzheimer's Disease, including APP [16-18], BACE1 [19-23] and microtubule associated protein tau, MAPT [24-26]. In all these works changes of miRNA expression were correlated to AD pathology, without, however, to determine whether the dysregulation of these microRNAs is cause or consequence of the disease. During the last years great progresses have been made to profile miRNA expression in several regions of human AD brains. Several miRNAs were identified to be upregulated and/or downregulated, but discrepancy in diverse profiles indicates an emerging need: i) large cohorts of sample ii) homogeneous tissue sampling protocols iii) complete unbiased and quantitative measurement of neuronal miRs.

Recently, the importance to explore RNA derived from well-characterized brain samples of several neurodegenerative diseases by application of RNA deep sequencing respect to other RNA profiling methods was evidenced. These studies suggested that respect prior annotations of miRNAs, the deep sequencing of small RNA species was less biased and show an unexplored class of small-non coding RNAs [27].

With the aim to overcome these limiting factors, more recently, the deregulation of specific miRNAs in the hippocampus of late-onset AD (LOAD) patients at Braak stages III and IV was shown. Among deregulated miRNAs, miR-132-3p down-regulation was revealed by next generation sequencing and confirmed from several independent laboratories [27-29,32]. The alteration of miR132-3p in Alzheimer's disease brain was suggested to be associated to neuronal cells containing hyperphosphorylated tau, and that a potential mRNA target of miR132-3p was the transcription factor FOXO1 [29]. Another miRNA, miR-34c was found to be increased in the hippocampus of both AD patients and AD mouse models, and identified as key regulator of learning-induced gene expression [30]. Next miR-34c was revealed to target a gene associated to risk factor in sporadic AD [31] named TREM2, which is reduced in human AD brains [32].

Use of circulating cell-free microRNAs as biomarkers for AD is of particular interest. MiRNA profiling from cerebrospinal fluid (CSF) samples from AD patients, was performed by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) [33]. This study performed on post-mortem samples evidenced a low correlation between miRNAs altered in CSF and miRNAs expression levels in brain regions affected in AD [33]. Looking for differential miRNA expression in either hippocampal tissue or CSF from AD patients and age-matched nondemented control subjects Muller et al., identified a

selected group of miRNA differentially regulated in hippocampus from AD patients. Interestingly, in CSF, expression analysis of this miRNA group was strongly influenced by the number of blood-derived cells in the sample [34]. Recently another study on miRNA expression in CSF from AD patients highlighted hsa-miR-27a-3p as a candidate biomarker for AD [35]. This work demonstrated that few miRNA were detectable in CSF ante-mortem respect to miRNA recovered in CSF post-mortem suggesting that in CSF post-mortem miRNAs potentially released from degenerating brain tissue were included. These investigations suggest that the modifications in miRNA levels can be detected in CSF, but the methodological approaches for a complete unbiased and quantitative measurement of CSF miRNAs are essential [36]. Moreover, an important topic about the CSF miRNA analysis is to individuate if selected miRNAs were associated to lipoproteins, exosomes or in complexes with RNA-binding proteins as Argonaute [37-39].

In conclusion, molecular and cellular neurobiological studies of the miRNA-mediated gene silencing in Alzheimer's disease, investigations on microRNAs in cellular and animal models, measurement of differential miRNAs expression in cerebrospinal fluid and serum as circulating biomarkers of AD, represent the exploration of a new frontier of miRNAs biology and the potential development of new diagnostic tests and genetic therapies for this neurodegenerative disease.

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