# The Role of miRNAs in Alzheimer's Disease

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Ever since the discovery of the DNA double-helix structure by Watson and Crick [1] in 1953, the standard pathway of information flow in a cell from DNA to messenger RNA (mRNA) to protein has been the dominant theme in molecular biology. However, the sequencing of the human genome has demonstrated that the transcriptional output of human genome is extremely rich in non-coding RNAs (ncRNA). [2] In contrast to ncRNAs, the biogenesis and function of small RNAs is well known and the best understood class of small RNAs is miRNAs. [3] In 1993, reports of the cloning and functional analysis of the first micro-RNA (miRNA), lin-4, surfaced the community of science by the pioneering work of Lee et al., and Wightman et al., 1993. They also provided a glimpse of things to come on the mechanism of miRNA production. [4,5] miRNA are ~22-nucleotide endogenous small RNAs processed from ~70-nucleotide hairpin structures in primary miRNA (pri-miRNA) transcripts by either the canonical miRNA pathway or the mirtron pathway.[6] The sequence of miRNAs is generally diverse, although a U residue is overrepresented at their 5'end. The human genome is predicted to encode as many as 1000 miRNAs, approximately 3% of the total number of genes [7], and these molecules inhibit gene expression by binding to complementary sequence in the 3' untranslated region (UTR) of target genes. [3]

Neurodegenerative diseases (NDDs) are a family of disorders characterized by progressive loss of neuronal function and structure, resulting in neuronal death in the nervous system. The pathological hallmark of many neurodegenerative diseases is a disturbed cellular homeostasis with accumulation of misfolded proteins in the form of cellular aggregates and the cytotoxicity of intermediate products, such as oligomers and protofibrils.[3,8] miRNAs deregulation is emerging as a key contributor to neurodegeneration by influencing most of the mechanisms responsible for NDDs. In the nervous system, miRNAs are essential in developmental timing, cell proliferation, cell death and patterning as well as function and identity of neural cell populations.[8] Neurodegeneration can also be considered to be an RNA disorder (Johnson et al., 2012) in which miRNA plays a major role.[9]

NDDs have become a daunting task for neurobiologist due to their enormous and growing social and economic implications in society. Thus, understanding the extensive spectrum of cell mechanisms could be relevant for the development of more effective therapies and diagnostic procedure for these disorders. At the one hundred eight anniversary of Alois Alzheimer's (1864–1915) first description of Alzheimer's Disease (AD in 1906), a colossal amount of scientific research effort into this common neurological disorder has been obtained, however many tricky gaps in our knowledge still remain.

AD, the most common form of dementia, is a complex neurodegenerative disorder characterized by the hallmark pathology of amyloid-β (Aβ) deposition, neurofibrillary tangle (NFT) formation, and extensive neuronal degeneration in the brain.[3] Aβ is a mainly 40–42 amino acid fragment derived from the membrane spanning amyloid precursor protein (APP) by proteolytic cleavage by the β-site APP cleaving enzyme (BACE1) and presenilin dependent γ-secretase.[3,9]

Recent research suggests that aberrant regulation of miRNA-dependent gene expression is closely associated with molecular events responsible for Aβ production, NFT formation, and neurodegeneration.[3] miRNA-29, miR-29b-1 and miR-9 down-regulation in the temporal cortex of AD patients was associated with up-regulation of BACE1 expression.[10,11] Diminished miR-107 levels in early stage of AD patients were associated with the up-regulation of BACE1.[12] Similarly, the most conserved and abundantly expressed nervous system-specific miR-124 has been shown to inhibit BACE1 expression in cultured rat PC12 cell lines and primary cultured hippocampal neurons, a cellular model of AD.[13] In hippocampus of APPSwe/PS1 mice, a well-documented model for AD, it was observed that miR-298 and miR-328 binds to the 3'-UTR of BACE1 mRNA causing a direct inhibition. It was also viewed that their expression was decreased with aging, signifying the altered levels of these miRNAs may deregulate BACE1 and sequentially, lead to increased Aβ formation and disease progression.[14] Now, as BACE1 is a target for both miRNAs and rate limiting enzyme for Aβ production, these results imply correlative mechanisms.[8]

Direct regulation of APP gene expression has been identified, and is mediated by miRNA binding to specific sequence in the 3'UTR. These include miR-106a and miR-520c; members of miR20a family (e.g., miR-20a, miR-106a/b, miR-17) [3,15]; miR-16 [16] in AD patients. In mouse models, miR-153 shows deregulation of APP in cerebral cortex.[17] These data imply that critical genes in AD could be regulated by multiple miRNAs.[8] Nuclear factor-kappa B (NF-kB) sensitive miR-146a, which targets complimentary factor H (repressor of inflammatory response), seems to be up-regulated in AD hippocampus and temporal cortex, leading to increased Aβ formation.[18]

Investigation for miRNA-binding sites in 3'UTR region of human tau mRNA displayed a direct inhibition of human tau by miR-34a. Hyperphosphorylation of tau causes insoluble aggregates into the cytoplasm of neurons where it gives origin to intraneuronal protein aggregates (NFTs).[3,19] A study showed upregulated expression of miR-9, miR-128 and miR-125b in the hippocampus of AD brains.[20] De-regulation of IGF-1-mediated signaling has been correlated with AD. IGF-1 function in the brain includes Aβ clearance from the brain and phosphorylation of tau. The expression of miR-98 negatively correlates with the IGF-1 expression level in mouse model of AD. Furthermore, over-expression of miR-98 in cellular model of AD is responsible for the down-regulation of IGF-1, enhanced Aβ production, and tau phosphorylation.[3]

The usage of 3'UTR region as potential target for modulating levels of BACE1 and APP is fascinating but the miRNA-based drug development is still in its infancy. It is tantalizing to target the miRNA itself to ease disease onset or progression.[21] Current drug discovery approaches in AD have focused on preventing Aβ formation or increasing "normal" APP processing through the inhibition of γ- and β-secretase activity or the activation of α-secretase activity; removing existing amyloid deposits via immunotherapeutic approaches. Now, the mRNA field has moved to the same direction. However, the question is whether these different approaches will result in clinically viable therapies and the blood brain barrier (BBB) remains an enormous hurdle for drug delivery in brain.[3]

Based on disease-associated changes in miRNA levels, one could potentially use changes in miRNA expression as biomarkers of aging and age associated processes such as neurodegenerative disease. They offer several advantages over mRNA or protein, including increased stability and biological relevance in many different ways. [3, 21]

A clearer understanding of how miRNAs influence the initiation and progression of AD and related neuropsychiatric disorders may not only reveal fundamental insights into the causes of these devastating human neurological disorders, but should also provide novel pharmacological strategies for advanced and efficacious intervention in the future clinical management of AD. We need to further elucidate the entire picture of the pathophysiological interaction among miRNAs, and proteins in AD brains. In conclusion, many scientific question remains to be addressed before using miRNA as therapeutic or diagnostic procedure.

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