Mechanisms Underlying Dysregulation of miR-132 in Alzheimer’s Disease

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Abstract

Abbreviations: CREB: cAMP-Response Element Binding Protein; DGCR8: DiGeorge Critical Region 8; ERK: Extracellular Signal-Regulated Protein Kinases; FOXO: Forkhead Box 0; ITPKB: Inositol-Trisphosphate 3-kinase B; MAPK: Mitogen-Activated Protein Kinase; MSK: Mitogen- and Stress-Activated kinases

Opinion

Alzheimer’s disease (AD), the most common format of dementia, is an increasingly prevalent and complex neurogenerative disorder in the elderly and among the leading causes of a miserable life quality and death worldly and characterized pathologically by both abnormal plaques consisting of aggregated amyloid β (Aβ) and neurofibrillar tangles of hyperphosphorylated tau [1]. microRNAs (miRNAs), small non-coding RNAs that regulate the translation of targeted mRNAs, are predicted to regulate up to 90% of the genes in humans, suggesting that they may control every cellular process in all cells and tissues of the human body [2]. Not surprisingly, alterations of individual miRNAs have been implicated in the AD pathological condition. The number of miRNAs is dysregulated in the AD disease conditions. Several neuroprotective miRNAs, especially miR-132, are downregulated in the AD patient brain, while several neurodegenerative miRNAs are upregulated in the same AD context [3]. Identifying what reasons and mechanisms cause the differentiative expressions of miRNAs may be key to the understanding of AD pathogenesis and the approaching of miRNAs for the AD therapy. Here we take miR-132 as an example to briefly discuss what mechanisms mediate its dysregulation under Alzheimer’s conditions.

Interplay of miR-132 with AD: miR-132 is specifically expressed and enriched in mammalian brains [4]. miR-132 and its parologue miR-212 gene locates in human chromosome 17. Mature miR-132 sequences of 22 base pairs are processed from its precursor sequence of 66 nucleotides. Human miR-132 consists of two homologous miRNAs, i.e., miR-132-5p and miR-132-3p. The latter is a significant part of the miR-132/212 cluster [5]. Several lines of evidence show that miR-132-3p is downregulated with pathologic AD and associated with neuritic Aβ plaques and neurofibrillar tangle pathologies in AD brains [6, 7]. miR-212/132 deficiency in a mouse model leads to impaired memory, enhanced tau pathology, and excessed Aβ production/senile plaque formation as seen in AD patients. Mechanism study shows that miR-132 can target and downregulate tau, MAPK, sirt1, FOXO1a, ITPKB, PTEN, and FOXO3a, which are implicated in tau production, splicing, and phosphorylation [8-10], Aβ metabolism and deposition [8,9], or programmed neuronal death [11]. Interestingly, miR-132 is
Although Biogen will pursue a regulatory approval for aducanumab because this antibody targeting amyloid in the Phase III EMERGE trial has met its primary endpoint, showing a significant decrease in clinical decline, miR-132 may still offer hope for the novel Alzheimer’s treatment [16], but we have to know how to target miR-132 for Alzheimer’s therapy because miR-132 is a multifaceted miRNA:

a) More than a dozen targets for miR-132 have been identified beyond the central nervous system [23];

b) Besides as the mediator to regulate neuronal differentiation and maturation and to participate in axon growth, neural migration, and plasticity, miR-132 is implicated in much non-neuronal functioning such as inflammation and angiogenesis [5,24]; and

c) miR-132 may induce neuronal apoptosis and enhance tau phosphorylation under certain AD conditions [25]. Therefore, the investigation of mechanisms underlying alteration of miR-132 in AD may not only help us understand the AD pathogenesis but also provide promising therapeutic targets for AD.

Only understanding of the mechanisms underlying dysregulation of miR-132 can help us to correct such a dysregulation, which may serve as more effective therapeutic strategies to address and modify AD pathological processes.

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References


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