CIRCULATORY MICRO RNA IN ALZHEIMER’S DISEASE

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ABSTRACT: Alzheimer's a neurodegenerative disorder characterized by progressive memory decline, multiple cognitive abnormalities and intellectual impairments. In the present scenario there is no drug available due to its discrete way of pathogenesis. Presently research is mainly focused on biomarker identification to know exact pathogenic pathway of Alzheimer's disease, to develop more precise therapeutic and for disease model development for better understanding of disease progression mechanism. After discovery of micro RNA micro prove as potential biomarker as they are found in circulatory bio fluids, such as blood and blood components, serum and plasma. MicroRNA is the part of non-coding genes regulates multiple target genes post-transcriptionally thereby able to target different pathway, signaling, hence may be act as cause or cure of the disease. Here we are summarizing microRNA genomics, biogenesis, and its contribution in pathogenesis of Alzheimer's disease, use of circulatory microRNA as a diagnostic tool for disease identification.

1. INTRODUCTION

In the society as the life expectancy of the people gets longer, the burden of cognitive impairment in society becomes increasingly important. Alzheimer disease (AD) is declared as progressive neurodegenerative disorder a most common cause of cognitive impairment among the elderly population. Currently, over 46.8 million people live with dementia worldwide, and this number is estimated to increase to 131.5 million by 2050. AD has huge impact on economy as estimated total worldwide medical cost of dementia in 2015 was $818 billion, and it will become a trillion-dollar disease by 2018 (1World Alzheimer's Report). Dr. Alois Alzheimer (1864–1915), a German psychiatrist and neuropathologist was the first person who depicted the Alzheimer’s diseases which
is multifactorial pathogenic disorder starts perniciously and evolves over several years prior to the expression of clinical signs and symptoms, linked to the age, gender (females are more likely to be affected), genetics (e.g. APOEε4 gene variant), nutritional levels, and Down syndrome’s. Alzheimer’s disease AD has two forms which are an early-onset familial which accounts for nearly 5% of all AD cases and is caused by rare genetic mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes (2) Bertram L and (ii) late-onset which accounts for the remaining 95% of all sporadic AD cases, including lifestyle, diet, environmental exposure, Type 2 diabetes, stroke, apolipoprotein allele E4, and several other genetic variants, are known to be involved in late-onset AD. Therefore, there is requirement of new therapeutic approaches to cure this disease. As it has become a global concern and threatens to impact heavily at both the social and economical level. Lots of researches are going on for disease identification (as by means of biomarker; identification at different level as in CSF, peripheral circulation and in brain tissues), progression (by knowing mechanism of progression of disease) and involved metabolic pathway (that will contribute in severity of this disease). By knowing, above scientist can be able to design an animal model for progression of this disease, on which they can be able to perform therapeutic interventions of, drugs that will target molecular switches that contribute progression of disease. There are lots of researches which are going on to identify Alzheimer’s in its prodromal stage which is mild cognitive impairment (MCI) appears as a transitional cognitive level between normal ageing and dementia having impairment in single domain (mainly memory impairment) forms the basis approximately all type of dementia. It is a condition in which an individual has mild but measurable changes in thinking abilities that are noticeable to the person affected and to family members and friends, but do not affect the individual’s ability to carry out everyday activities. People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer’s and other dementias than people without MCI. Revised criteria and guidelines for diagnosis of Alzheimer’s disease published in 2011(3,4,5) suggest that in some cases MCI is actually an early stage of Alzheimer’s or another dementia. However, MCI does not always lead to dementia. In some individuals, MCI reverts to normal cognition or remains stable. In other cases, such as when a medication causes cognitive impairment, MCI is mistakenly diagnosed. Therefore, it’s important that people experiencing cognitive impairment seek help as soon as possible for diagnosis and possible treatment. MCI can be categorized as (i) amnestic MCI – predominantly a decline in memory capacity, but largely retaining intact executive functions, and (6,7 Schmand B Peterson RC) (ii) non-amnestic MCI – characterized mainly by decline in language presentation, visuospatial ability, and executive functions [8 Taragano FE]. Generally AD identification is normally based on CSF and PET imaging (9) Richard E but due to high costs of PET and invasive nature of CSF collection currently preclude their utility for routine clinical testing. So a non-invasive and high-throughput blood-based test is required for improved population-based screening and patient care in order to refer patients for further examination. So a
non-invasive and high throughput blood-based test is required for improved population-based screening and patient care in order to refer patients for further examination. Earlier blood is studied for protein based identification of disease but after the discovery of miRNA the paradigm of disease identification shifted towards it. The downregulation of gene expression by miRNAs is now commonly believed to be an important and universal mechanism involved in most cellular signaling pathways. MicroRNA mediated processes have been found dysregulated in various human pathologies, and most importantly, in carcinogenesis. One of the essential features of miRNAs is their ability to interact with multiple targets. Each miRNA can regulate hundreds of protein encoding genes, and vice versa, each structural gene can be a target for multiple miRNAs (miRWalk) (10) Felekis K. CSF and PET used to identify neurodegenerative disease markers, but to do so, they need to be executed late in disease progression - too late to initiate successful preventive or effective therapeutic measures (9). Therefore, a less invasive method to diagnose AD and other neurodegenerative diseases much earlier than current methods is needed, and one promising alternative is through the use of biomarkers. One such promising biomarker for AD is circulating miRNAs. The purpose of this article is to discuss latest developments in circulating miRNAs and their possible role in early, noninvasive identification and assessment of AD.

Micro RNAs

miR a 20-54 nucleotide(ntd) long noncoding RNA function post-transcriptionally and shapes the transcriptomic structure of cell and by doing so casts the molecular genetics and phenotype of human CNS health and disease.(11-14) Alexandrov PN Clement C Schmidt U Of the known 2550 mature unique human miRNA only specific miRNA population are appear to be enriched in different anatomical compartment within CNS.(15-17) As of other nucleotide sequence it also has phosphate backbone assumes the shape of negatively charged rod in neutral pH solution with additional topological feature characterized in part of that miRNA unique ribonucleotide sequence and because miRNA are composed of different ribonucleotide a 22 ntd may assume having about 1013 combination of which only 2x103 different mature miRNA in human suggest an extremely high evolutionary selection to utilize only specific ntd sequence that will yield biologically productive miRNA-mRNA interaction.(18-19). The abundance, speciation and complexity of these highly selected miRNA may vary among the different human population in aging, health and neurological diseases. There are number of research paper which describes about the abundance, speciation and complexity in AD and aging CNS (20-21).
Genomic organization and biogenesis

5% of the human microRNA found clustered in the genome. Clustered gene have tendency to to form polycistronic transcript which combine with common transcription direction. Their location can be intergenic or intragenic. Microrna with intragenic position usually about half of the microRNA genes are associated with known transcription unit. Origin of microRNA starts with the transcription product of long primary nucleotide chain as pri-microRNA by RNA polI (23) and in rare cases by RNA polII in the rare cases. Microrna is the one of the part of non coding region with the ability to regulate 30% gene expression of mammalian genes. Some micro RNA originated by a common promoter, about 42-48% of all microRNA originate from polycistronic units which have multiple discrete loops from which mature microRNA are processed means promoter of these genes have some similarity in their motifs of the promoter of other genes transcribed by RNA pol II such as protein coding genes that are variant of mature microRNA known as iso microRNA. Around 6% of the microRNA exhibits RNA editing(iso micro RNA), generated by site specific modification of the reference microRNA which increases diversity and scope scope of microRNA action action beyond that implicated in the genome alone. Primary micro RNA transcribed by either RNA pol II or III are further processed by drosha in the nuclease which process pri-microRNA to 70 ntds pre-microRNA which get exported to the cytoplasm in thermodynamic dependent manner via exportin 5 proteins. In cytoplasm dicer cleaves pre-microRNA to the 20 ntd mature micro duplex intermediate m (24). Mature microRNA now assembles with other protein and form micro RNA containing ribonucleotide
particle, similar with RISC. As MiRNP for microRNA guide this complex to the target mRNA via seed sequences. In animals microRNA partially binds to the multiple partially complementary sites in the 3’UTR. Seed sequence nucleate binding between target and mRNA. A perfector near perfect complementation leads to the direct inhibition of the protein accumulation without strongly affecting mRNA level.

**Mechanism of miRNA Gene Regulation**

![Image of mRNA degradation and regulation](image-url)

Figure 2: Mechanism of Micro RNA gene regulation

MiRNP (microRNA protein) and the mRNA interaction can have several consequences. These consequences include either direct or indirect effects on translation. Direct effects occur either by means of inhibition of initiation of translation, that results in prevention of ribosome association with the target mRNA, or by means of inhibition of translation post-initiation. During post-initiation repression, a premature ribosome drop off, an event of slowed or stalled elongation, and cotranslational protein degradation which, a repressed mRNA seems to be present in form of polysomes: i.e. targeted mRNA is associated with multiple ribosomes occur during the course of translation. Apart from the direct effects on translation (or protein accumulation), miRNPs can have other effects on targeted mRNAs, which involves deadenylation, that might result in degradation (an increased turnover). De-adenylation and degradation events might take place in P bodies (denoted by P), a cytoplasmic foci that are enriched with the factors required for the mRNA degradation. There is also a possible that miRNA-targeted mRNAs might be sequestered from the translational machinery and degraded or stored for subsequent use. Alternatively, targeted mRNAs might be
sequestered as a consequence of inhibition of initiation of translation.

**Role microRNA in human brain development and function**

Brain is composed of complicated intricate network formed by various types of cells (neuronal and non-neuronal). Micro RNA has different expression and penetrance in all the organisms. It is found that around 70% of total micro RNA expressed in the brain (36) with brain specific or brain enriched expression. These miRNA have different location and target so perform different function in the brain. Diversity of miRNA in brain suggests a shear connection between the biogenesis and dynamics of the action, regulatory potential of the miRNA and complexity of the brain there lots of the evidences which suggest role of miRNA in the brain. As loss of the Dicer gene in the nervous system of the animal models demonstrates micro regulatory role over controlling neuronal proliferation, migration, precursor fates (37,38,39,40,41) and serve important role in brain development and function(42,43). Strak investigates role of Dicer deficiency in mice model of Schizophrenia (44). Sempere et al. conducted a expression study in mice and human and found a group of microRNA (miR-7, -9, -9*, -124a, -124b, -125a, -125b, -128, -132, -135, -137, -139, -153, -149, -183, -190, -219) have role in regulation of neuronal differentiation, maturation, and or survival(45). These micros RNA are found conserved in mice and human. Above mentioned miRNA are found conserved so, play conserved role in establishment and maintenance of the cell or tissue types of the brain. Some of the microrna are region specific as miR-9 and miR-132 are restricted to the brain hippocampus region and medial frontal gyrus. MiR-124 and miR-128 are specific only for the neurons, miR-23, miR-26 and miR-29 are expressed in the astrocytes(46). MiR-195 have differential expression respective to the age as age increases miRNA expression decreases (47). Apart from development, aberrant microRNA expression has been discovered in human CNS (central nervous system) diseases including brain tumors in the past decade.

**Advantages of using miRNA as a biomarker**

There are lots of advantages of using microRNA as a biomarker. It has ease of detection and extreme specificity, it can be preserved in formalin fixed, paraffin embedded tissue and in fresh scrap frozen specimen (48). Micro RNA isolate and profiled by different method such as for total mRNA purification (column filtration protocol, tri reagent composed of acid phenol in combination with guanidinium thiocyanate and chloroform) and different miRNA profiling techniques (sequencing, microarray and quantitative reverse transcription polymerase chain reaction (qRT-PCR) based method.

**Micro RNA secretion in bio fluids**

MicroRNA are able to release out from the cell to the extracellular environment as by binding with RNA binding proteins or through in cell derived plasma microvesicles such as exosomes (49, 50). Hence microRNA expression profiling in extracellular environment or medium reflects the
physiological state of the biological system. There are five modes of secretion of microRNA in extracellular circulatory bio fluids. 1. Micro is bound to high density lipoprotein (HDL) particles in non vesicle form. 2. They form an interesting complex with Ago2 proteins. 3. They are placed in exosomes. 4. They are encapsulated in microvesicles. 5. Micro accumulate in opposite bodies. Exosomes are cell membrane derived vesicles having approximate size of about 50-100nm in diameter consider as natural biological nano vesicles or multivesicular bodies that originate from endosomes and by making fusion with plasma membrane get excreted out from the cell to extracellular medium. Microvesicles are slightly larger vesicles (100-400 nm) originate from outward budding or blebbing of plasma membrane. Microvesicles (MV) are secreted by different cell types such as neurons muscle cells, inflammatory cells and tumor cells. Platelets are considering to major source of microvesicle. The main function of microvesicular bodies and exosomes is to facilitate intercellular communication and transportation of various biomolecules such as DNA, RNA, and proteins. Exosomes are considered diagnostic molecules for some reasons such as due to ability to cross the Blood brain barrier through transcytosis (so able to cross endothelial layer and circulate in biofluids which is essential for diagnosis of neurodegenerative disorders). Microrna in exosomes present in its protected RNase form. Micro RNA when transported out from the cell, some part of argonaute protein complex also found in microvesicles. Arroyo et al. found that 90% of microRNA in MVs is bound with Argonaute (Ago2 protein complex for example: miR-122 is found in liver enriched cellular environment and has been exclusively detected in Ago2 protein complexes. Binding of Ago2 protein complex provides more stability to the micro RNA which helps micro RNA way of secretion, transmission for one cell to another cell and circulation in biofluids. The exact mechanism of action and lots of further research are needed to envil the link between microRNA and their secretion.

**Microrna biochemical contribution to the pathogenesis of Neurodegeneration**

AD is neurodegenerative disease, neurodegeneration is a term that refers to the different trophies. In course of neurodegeneration neurons losses their connections and die prematurely. Although highly relevant to physiological cell death, h nosological ND entity has its own set of pathological processes, some of which presumably unique. However there are six general ideas that are relevant at least circumstantially,

(i) Most NDs are not inherited in patterns that reflect simple Mendelian genetics

AD is a subtype of neurodegeneration which is inherited in sporadic manner influenced by alleles with limited genetic penetrance, or are caused by genetic and/or environmental influences as yet uncharacterized. Above information shift our paradigm of away from traditional gene which are constitute only 1-2% of human dna and towards the other ~50% of transcribed DNA about which we are mostly ignorant.
(ii) Brains of human neurodegeneration patients show evidence of chronic stress
Cellular stress is evidenced in ND (60, 61) this initiates a cascade of events that are involved in cellular death and hence causes neurodegeneration.

(iii) Neurodegeneration may be exacerbated in the clinico biological sense by the aberrant stimuli of developmental pathways
It was found that some biochemical pathway is upregulated during normal brain development but downregulated during normal adulthood are aberrantly upregulated during neurodegeneration. These include pathways involved in cell--cell signaling, cell division, neuroplasticity and apoptosis. In the case of the microtubule-associated protein tau (MAPT), there is an mRNA splicing variant that is more highly represented both in early development and in some neurodegenerative diseases (62, 63). Furthermore, the developmentally up-regulated phosphorylation of MAPT is also up-regulated in AD neurofibrillary pathology (64, 65).

(iv) RNA is pathologically altered in NDs
RNA is very fragile even in controlled condition. As during neurodegeneration brain RNAs becomes pathologically altered (66, 67) but include aberrant RNA oxidation, RNA degradation, altered RNA splicing and ribosomal changes which cause mRNA translational frame-shifting abnormalities.

(v) Human NDs are chronic conditions that last for decades rather than just for several years
On clinical diagnosis it is found that neurodegeneration is not takes few years to develop symptoms rather it about a decade to develop its symptoms. AD as an example, the time from patient's’ clinical diagnosis to death is typically ~8 years (68). The underlying pathological processes of AD occur over many decades. Persons at risk for developing AD in their seventh or eighth decade already show brain metabolic abnormalities by PET scan even in their third decade of life (69, 70). This shows that ND pathology involves a long evolving shift in cellular equilibrium, which could be “tipped” even by subtle genetic and/or environmental influences.

(vi) Pathogenetic mechanisms of ND involve multiple distinct steps
Neurogenration is not a consequence of one pathological process it involves a sequential progression of pathological processes that result collectively in neuronal death and/or compromised connectivity. In the case of AD, the most prevalent hypothesis is the “amyloid cascade hypothesis” (71, 72) and both neuritic amyloid plaques and neurofibrillary tangles are apparently required to produce the advanced clinical stages of the disease. These features of NDs dovetail on some of the known characteristics of miRNA biochemistry in the brain. MiRNAs derive from “non-traditional genes”; are related to pathways of cellular stress and neurodevelopment; may be altered by the changes seen in ND brains such as oxidation; and may ultimately contribute to step(s) that culminate in chronic brain diseases.
Overview of micro RNA involved in metabolic pathway of Alzheimers pathogenesis (73)
### Overview of circulatory micro RNA in AD

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<td>CDK6</td>
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Circulatory micro RNA reported in AD

Alexandrov et al. (2012) (83)
Denk et al. (2015) (84)
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**MiR-146**

MiR-146 family comprises miR-146a and miR-146b. Literature shows that miR-146a is upregulated, while miR-146b is downregulated, in AD brains (85, 86, 87, 88). The mechanism and functional consequences underlying this difference in regulation remain to be elucidated. Both miR-146a and miR-146b are mainly known as immune system regulators (89), which could inherently be associated with AD progression, as the expression or activation of numerous inflammation effectors has been documented in AD patients. One of these factors, IL-1, is overexpressed at early stages in AD, and was shown to modulate miR-146a/b expression (90, 91, and 92). IL-1 through the NF-κB pathway.
transcription pathway induced the expression of miR-146a, but not miR-146b (93, 94, and 95). MiR-146a target genes, including RANTES and IRAK1 whose expressions are altered in AD brains, are directly involved in inflammation (96). Based on these observations, it is thus tempting to speculate that miR-146 misregulation is both a consequence and a cause of the inflammatory response in the AD brain, which could have repercussions at both early and late stages of the disease.

**MiR-15**

MiR-15/107 gene expression is specifically responsive to glucose metabolism and PPAR signalling. MiR-15/107 miRNAs are dysregulated early in AD pathogenesis, before cell type changes (i.e., neuronal loss) is observed. MiR-15/107 miRNAs are important to assess comprehensively (as opposed to being analyzed one-by-one) because miR-15/107 miRNA gene regulatory activities overlap strikingly. MiR-15/107 miRNAs regulate specific neurodegenerative disease genes (including BACE1), linking miRNA expression with neurodegenerative disease pathology (97).

**MiR-9**

Mir-9 is encoded by 3 different genes, found at the loci 1q22, 5q14.3, and 15q26.1, all of which contain a CpG island in their promoter region (98, 99) which is found as circulatory miRNA in serum. Alzheimer's disease pathology occur by MiR-9 hypermethylation and its respective downregulation in expression which has been demonstrated in several cancer studies (100, 101, 102, 103, 104). MiR-9 expression has been found abundantly elevated in the fetal hippocampus, although mir-9 levels have been found to be downregulated in postmortem brains from patient with AD (105,106,107,108). In Vitro studies examined downregulation of amyloid beta (Ab) in hippocampal cell cultures and in transgenic Ab42-depositing APP23 transgenic mice (105) and also downregulated miR-9 was noticed in presenilin 1 knockout mice, coinciding with severe developmental brain defects (109). The repertoire of miR-9 targets expands to fibroblast growth factor receptor 1 (FGFR1), CDK6, caudal-type homeobox 2 (CDX2), NFKB1, and sirtuin 1 (SIRT1), the latter of which provides feedback to the level of epigenetic control, via its HDAC activity (110, 111,112, 113).

**MiR-125b**

MiR-125b is encoded by 2 genomic loci, miR-125b-1 and miR-125b-2 which is brain enriched. MiR-125b has been shown to be significantly up-regulated in human neurodegenerative disorders including AD (114,115). This upregulation has been proposed to contribute to astrogliosis and deficits in the cell cycle that are characteristics of degenerating brain tissues (116). Interestingly, miR-125b has been identified as a suppressor of the Hedgehog pathway by targeting the upstream pathway activator smoothened, and its downstream transcription factor glioma-associated oncogene family zinc finger 1 (GLI1), with the latter one being upstream of DNMT1 and DNMT3A expression, thereby contributing to indirect feedback modulation of epigenetic mechanisms (117,118).

**MiR-200**

miR-200 family is grouped in 2 clusters, namely miR-200b/200a/429 and miR-200c. MiR-200c
regulation by DNA methylolation is found to be evolutionarily conserved in humans and mice (119). With respect to AD, miR-200a levels were increased in peripheral blood mononuclear cells of patients with AD (120); however, its function in AD pathology has yet to be determined. A specific role has been proposed for miR-200b in the regulation of zinc finger E-box binding homeobox 1 and 2, both of which are involved in the regulation of E-cadherin expression, a type-I transmembrane protein associated with cell-cell adhesion and decreased accumulation of total secreted Aβ (121, 122, and 123).

**MiR-181c**

MiRNA is located at 19p13.13 (124). MiR-181c was reduced in the CSF from patients with AD (125). MiR-181c loss is correlated with increased serine C-palmitoyltransferase and Aβ levels in human AD brains, whereas miR-181c is in turn downregulated by Aβ in human primary astrocyte and murine primary hippocampal cultures (126,127). Above observations are further supported by both AD human and APP23 transgenic mouse brains, which demonstrates that Aβ deposits are associated with the downregulation of many brain specific miRNAs, essential in neurogenesis (128). MiR-181c has also been suggested as an additional repressor of SIRT1 expression, thus being a part of the reciprocal communication of miRNAs and epigenetic mechanisms (129). Target genes of miR-181c extend from TGFβ1 to NOTCH4 and V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), implicating miR-181c in various physiological and disease pathways and regulatory feedback loops (128,129). A potential role for miR-181c has furthermore been suggested in the regulation of one of its direct targets, tumor necrosis factor alpha, in which the miRNA’s repressive function is attenuated by hypoxia and/or neuronal injury involving microglial activity (130, 131).

**MiR-137**

MiR-137 is an intragenic miRNA that is directly overlapped by a CpG island, located at 1p21.3. Downregulation of miR-137 levels, because of either genetic or epigenetic alterations, increases serine C-palmitoyltransferase, an important enzyme in de novo ceramide synthesis and associated regulation of Aβ levels, therefore providing a mechanism for the elevated risk of AD (129). Epigenetic regulation of miR-137 expression involves MeCP2 and co regulation by SOX2, a core transcription factor in stem cells (130). MiR-137 is furthermore involved in neurogenesis by targeting CDK6 (134), promoting neural differentiation of embryonic neural, oligodendroglialoma, and glioblastoma stem cells. Interestingly, a recent study also demonstrated significant enrichment of miR-137 at the synapses of cortical and hippocampal neurons, suggesting a role of miR-137 in regulating the synaptic protein synthesis machinery (135). Underscoring its importance in neurogenesis, miR-137 targets the mind bomb 1 protein, an ubiquitin ligase essential in neurodevelopment, through the conserved target site located in the 30-UTR of mind bomb 1 protein mRNA (136). In addition, the histone lysine-specific demethylase 1 a transcriptional corepressor of nuclear receptor TLX, is a downstream target of miR-137. TLX, on the other hand, is an essential regulator of neural stem cell self-renewal and
represses miR-137 expression by recruiting histone lysine-specific demethylase 1 to the genomic regions of miR-137, thus forming a regulatory feedback loop to control the dynamics between neural stem cell proliferation and differentiation during neural development (137).

MiR-26a and miR-26b
MiR-26a and miR-26b were found altered in peripheral blood in AD patients (138) of both miRNAs can regulate the expression of the neurotrophin BDNF, a main player of adult brain neurogenesis and synaptic plasticity maintenance (139).

MiR-34a
In human AD patients the level of miR-34a was found elevated. MiR-34c (140) is belongs to the miR-34 family. MiR-34 is studied in different aging organism as mice and human. Mutation or loss of function in miR-34 correlates with accelerated aging and neurodegeneration studied in drosophila. There are member of miR-34 family each of them have a different regulatory role. MiR-34c level is found enriched in hippocampus region of the brain and its expression is further upregulated by aging and amyloidosis in AD patient’s brain. MiR-34 also target SIRT1 (141) which is responsible to restore memory. up regulation of miR34c causes decrease in SIRT1 and hence causes memory dysfunction and vice versa observed in mice model(142). So it is evidenced from above and in-vitro experiments that the miR-34 family have control over several developmental and age-related metabolic pathways. Conceivably the targets of miR-34 are multiple and their functions may vary temporally and impact the aging process and disease.

MiR-107
MiR-107 was found increased in blood of AD patients (143). Altered miR-107 was associated with cytoskeleton pathology in a transgenic mouse model of AD and with granulin/progranulin expression regulation in vivo and in vitro, with implications for brain disorder (144,145).

MiR-29
Evidence that loss of the miR-29a/b-1 cluster is linked to sporadic Alzheimer’s disease was provided by He´bert et al 2008(146). The study investigated possible regulators of the BACE1/b-secretase. BACE1 or APP may conceivably contribute to Aβ in sporadic Alzheimer’s disease cases. BACE-1 processing of APP is essential to initiate Aβ generation, which is then promoted by the γ-secretase. MiRNAs that are potentially involved in the control of BACE1 expression (miR-29a, 29b1) were found to be downregulated in brains of Alzheimer’s patients that also showed high BACE1 levels. BACE-1 expression and APP processing. Also, the miR-29 cluster has important roles in the brain related to aging and disease. Dendritic spine remodelling which is regulated by targeting ARP2/3 actin nucleation complex, from miR-29 gene cluster. This is especially important for structural neuronal plasticity (147).
2. CONCLUSION

As micro RNA are proved to be notable diagnostic tool for biomarker identification study due to its wide range of availability, involvement in different metabolic process involvement and due to degeneracy of regulation of gene expression. In AD there is differential expression of micro RNA. Some micro RNA are specifically expressed in specific area of the brain and some of the micro RNA are involve in specific gene expression. Many of the circulatory micro RNA are act in degenerate manner as target more than one or two target protein. In wholistic view, they target expression of many gene and downregulate or upregulate these gene so they act as a positive tool for the biomarker identification in AD. Circulatory micro RNA biomarker identification is also a blood based as of proteomic blood based biomarker identification but the former one is transcriptomic level expression study. Micro RNA study is prefer over CSF and PET study due to non-invasive nature of the CSF and high cost of the PET imaging. Micro RNA based biomarker identification can also be used for biomarker identification in the prodormal stage of AD which is mild cognitive impairment categorized under amnestic and non-amnestic MCI. Many researchers are now exploring the role of miRNAs in AD which are high fueled, at least in part, due to the fact that gene dosage effects and gene expression misregulation are inherently linked to both genetic and sporadic AD. Current literature as well as bioinformatic predictions suggests that miRNAs could function either upstream, concomitantly, or downstream of Aβ and Tau pathologies to coordinate the cascade of events leading to the severe neurodegeneration observed in AD patients. These provides the growing interest in miRNAs and other non-coding RNAs in general, combined with the advancements in RNA sequencing technology, these can anticipate various follow-up studies addressing the role of miRNAs in AD and other neurodegenerative disorders. Above literature will help to answer additional questions concerning the use of miRNAs as potential diagnostic markers, either alone or in combination with Aβ and/or Tau.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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