Review Paper:

Unraveling the Role of Non-Coding RNAs in Alzheimer's Disease

Siragam Satyalakshmi
Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Visakhapatnam 530049, INDIA
satyalaxmi148@gmail.com

Abstract

Neurobiology provides profound insights into studying the molecular, cellular and systemic levels of pathophysiological processes, risk factors and potential therapeutic avenues associated with various neurodegenerative disorders. Alzheimer's disease (AMD) is a globally significant condition primarily affecting the elderly, necessitates an understanding of its connection to the nervous system. AMD poses a persistent challenge as an enigmatic neurodegenerative disorder impacting millions of people worldwide. Genetic approaches for the treatment and diagnosis of AMD offer distinct advantages compared to traditional treatments. This review shifts the spotlight to the intriguing realm of non-coding RNAs and their pivotal role in AMD pathogenesis. Non-coding RNAs constitute diverse class of RNAs which do not involve in protein synthesis but take significant part in regulation of genes and cellular mechanisms.

In recent years, emerging research has unveiled the substantial influence of various non-coding RNAs including microRNAs, long non-coding RNAs and circular RNAs, in the complex landscape of AMD. Non-coding RNAs have gained significant attention with their roles in mediating AMD-associated processes such as synaptic plasticity, amyloid precursor protein metabolism and oxidative stress. This review delves into the multifaceted functions of non-coding RNAs in AMD, shedding light on their regulatory mechanisms, their involvement in disease progression and their promise as diagnostic tools and therapeutic targets.

Keywords: Alzheimer's disease, Neurodegenerative, Genetic approaches, Non-coding RNAs, Diagnosis, Therapeutic target.

Introduction

Alzheimer's disease (AMD) is a gradually depleting neurological condition leading to progressive neurodegeneration, typically initiating in the entorhinal cortex within the hippocampus. AMD is primarily associated with advanced age, making it predominantly an ailment of the elderly. Globally, an estimated 24 million individuals are affected by dementia, a number projected to quadruple by the year 2060. The annual healthcare expenses linked to AMD are estimated at $172 billion. The incidence of AMD approximately doubles every five years after reaching the age of 65, with that occurrence rate increasing 10 % more after the age of 65 and it is 40% more after the age of 85. Above the age of 85, in most of the women, the AMD incidence rates are reported.[4,31,50]

Pathophysiology: The pathogenesis of AMD involves a complex and multifaceted process that unfolds sequentially over time. Although our understanding of the exact mechanisms is still evolving, the following provides a simplified overview of the sequential steps involved in the progression of AMD, emphasizing the deposition of beta-amyloid (Aβ) peptides and abnormalities in Tau protein as contributors to AMD progression.[53]

Amyloid precursor protein (APP) processing: The process initiates with gene expression from chromosome 21 for the synthesis of amyloid precursor protein (APP). APP undergoes two processing pathways: non-amyloidogenic or amyloidogenic. In the amyloidogenic pathway, enzymes known as beta-secretase and gamma-secretase cleave APP, resulting in the production of beta-amyloid (Aβ) peptides. The accretion of Aβ peptides stands as a hallmark of AMD[52] as illustrated in fig. 1A.

Aggregation of Aβ peptides: Aβ peptides exhibit a propensity to aggregate, forming toxic plaques in the brain. These plaques disrupt normal neuronal function and are considered key factors in the progression of the disease.

Tau protein abnormalities: Concurrently with Aβ aggregation, there is an abnormal phosphorylation of tau proteins. Tau is crucial for maintaining the structure and stability of microtubules in neurons. In AMD, tau undergoes hyperphosphorylation, leading to the formation of neurofibrillary tangles within neurons. These tangles disrupt the neuron's transport system and contribute to cell death (Fig. 1B).

Neuroinflammation: The brain's immune response is activated in response to the presence of Aβ plaques and tau tangles. Chronic neuroinflammation can result in further damage and neuronal cell death. Furthermore, the accumulation of Aβ and the presence of neuroinflammation lead to increased oxidative stress, neuronal cell death, synaptic dysfunction and ultimately, the progression of cognitive decline. As these sequential processes continue and more neurons are affected, cognitive decline becomes increasingly severe, manifesting in the clinical symptoms of

AMD including memory loss, disorientation and impaired decision-making. It is crucial to remember that each person may experience these processes in a different order and with different dynamics. There are still many aspects of AMD pathogenesis that are not fully understood. Researchers continue to investigate these mechanisms in the hope of finding more effective ways to diagnose, to treat, or even to prevent AMD.[16]

Impaired cholinergic function: According to the cholinergic hypothesis in the early stages of AMD, there is a damage of cholinergic neurons in the basal nucleus and the entorhinal cortex, with over 90% loss in the advanced stage.[34] Loss of memory in animal models due to unusual functioning of the cholinergic neurons, leads to AMD.[7] Cholinergic neurons damage in the basal forebrain and the loss of central cholinergic transmission lead to cognitive and non-cognitive symptoms in AMD patients.[34] Additionally, the cholinergic hypothesis is marked by a potential depletion in acetyltransferase concentration, responsible for acetylcholine synthesis in the cortex and hippocampus and the cholinergic neurons loss in the Meynert basal nucleus.[26] Cholinergic dysfunction and neuronal cell death disturb specific transmission systems, leading to deficiencies in acetylcholine, noradrenalin and serotonin.[13]

Genetic mechanism: While the majority of AMD cases are sporadic i.e. lacking a dominant genetic cause, rare mutations in the APP gene could happen, resulting in familial AMD.[47] The ApoE allele ε4 has been identified as a robust genetic threat for AMD development.[47,64] Individuals carrying the ApoE allele have a threefold increased risk of developing AMD.[28] The mechanisms linking ApoE with AMD are not fully understood, but it is suggested that there is a decrease in Abeta clearance in the brain in such cases.[28,30] Additionally, research indicates a high association between people with a genetic propensity to have AMD or similar disorders and those who have presenilin alleles (PSEN 1 and PSEN 2).[2] When the disease is genetically driven, PSEN 1 and PSEN 2 mutations, which are uncommon in AMD patients, are important. This is especially true in early-onset pathology, a rare type of the disease.[18]

Role of non-coding RNAs (ncRNA) in AMD: Conventional approaches in diagnosing and treating AMD face numerous challenges including delayed diagnosis, symptomatic relief without addressing root causes, the absence of disease-modifying therapies, limited treatment efficacy, invasive diagnostic methods and the risk of misdiagnosis. Genetic approaches effectively tackle the limitations of conventional AMD diagnosis and treatment. They offer early disease detection, the ability to deliver personalized and effective therapies, insights into potential targets for disease-modifying treatments, accelerated drug development through identification of specific molecular targets linked to Alzheimer's pathology, a deeper understanding of the complex genetic factors underlying the disease and the facilitation of more precise therapeutic strategies.

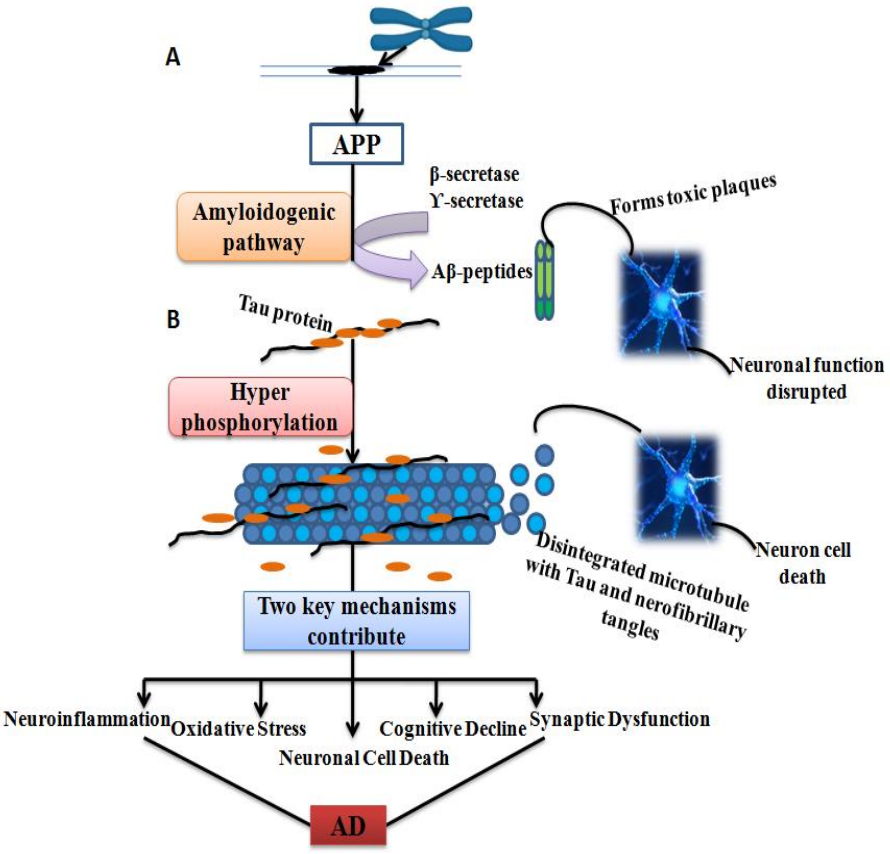

Figure 1: (A) Mechanism of APP processing, (B) Mechanism of abnormal phosphorylation of tau proteins

Given the multifactorial causes of AMD, it presents a diverse array of potential targets for gene therapy. Because of advancements in sequencing technology and whole genome analysis, many genes linked to AMD have been found. Strong evidence suggests that non-coding RNAs (ncRNAs) are important regulators of gene expression at the transcriptional and post-transcriptional levels, impacting a broad range of biological processes like differentiation, apoptosis, proliferation, self-renewal of stem cells, preservation of cell integrity, formation of synapses and responses to DNA damage.[62] Notably, changes in the expression patterns of ncRNAs have been connected to neurodegenerative diseases and brain aging. These RNAs are especially abundant in the central nervous system (CNS). The subsequent discussion explores the potential relationship between ncRNAs and AMD pathophysiology.

Non-coding RNAs - introduction and general regulatory functions: Recent research consistently unveils an expanding array of RNA types in more complex organisms that do not encode proteins, collectively known as non-coding RNAs. These RNA molecules include small nuclear RNAs that take part in splicing events with mRNA transcripts as well as classes of traditionally recognized translation-related RNAs such as transfer and ribosomal RNAs. Furthermore, ribosomal and transfer RNAs, among other smaller RNAs, are chemically modified in large part by small nucleolar RNAs. Housekeeping and regulatory non-coding RNAs are the two main categories into which non-coding RNAs fall. Regulatory non-coding RNAs are further categorized into two groups according to their length as long ncRNAs and short-chain ncRNAs.

Short-chain ncRNAs include circular RNAs, short interfering RNAs, microRNAs and piwi-associated RNAs.[51] Regulatory RNAs are crucial because they regulate gene expression in vital cellular systems and biochemical interactions. More than 200 nucleotides in length, long non-coding RNAs play a role in a number of biological processes such as X chromosome inactivation, mRNA stability, promoter-specific gene regulation and epigenetic control of chromatin modification. Fig. 2 illustrates different classes of non-coding RNAs and table 1 details the properties and significant functions of these ncRNAs.

Role of nc-RNAs in AMD pathogenesis: An expanding body of literature consistently points to the involvement of noncoding RNAs (ncRNAs), particularly miRNAs, circRNA, piRNA and lncRNAs in the pathogenesis of AMD. It has been shown that these ncRNAs contribute via different pathways to tau and amyloid β (Aβ) peptide accumulation, neuroinflammation, neuronal loss and other known patho-mechanisms related to AMD.

Roles of miRNAs in AMD pathophysiology: MiRNAs are abundantly expressed within the CNS exhibiting region-specific and age-dependent expression. Adult mice, for instance, show specific subsets of miRNA expression in the hippocampus and cortex. Neuron subtypes (e.g. glutamatergic vs. GABAergic neurons) and their cellular locations (e.g. distal axons vs. synaptic fraction) have an impact on the expression profiles of miRNA. MiRNAs are essential for neurogenesis, synaptic function, neuronal plasticity, memory and learning. miR 106a 5p/363 3p, miR 17 5p/92 3p cluster and miR 106b 5p/25 3p are shown to be significant during brain development.[6] For neurogenesis, axonal development and neuronal migration, miR 124 3p and miR 9 5p are essential.[42]

Beyond neurons in the central nervous system, microRNAs have an impact on a variety of cell types. For example, let 7b 5p and miR 125 5p regulate astrocyte differentiation while miR 338 5p and miR 138 5p are involved in oligodendrocyte differentiation.[46] In Aβ pathology, miRNAs impact APP and Aβ-producing enzymes. Abnormal Aβ production and metabolism contribute to AMD pathogenesis. Negative regulators of APP such as miR-101, miR-20a and miR-17 are implicated, with their unbalanced expression playing a role in AMD progression.[9] Certain miRNAs, including miR 16, miR 29a/b 1 and c, miR 186 and miR 195, show decreased expression in the brains of AMD patients and AMD mice.[63]

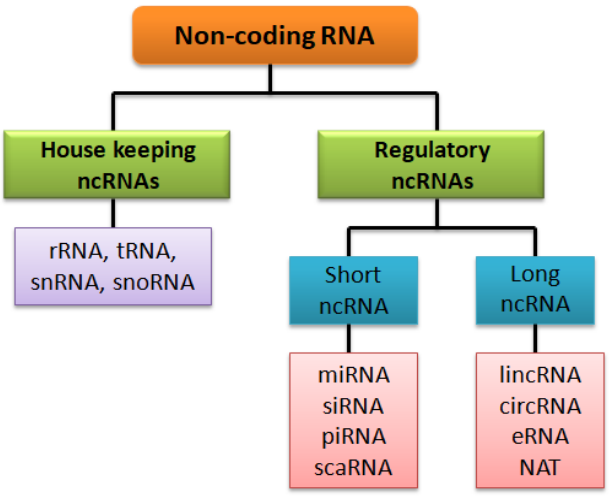

Figure 2: Types of noncoding RNAs

Table 1
Properties and important functions of ncRNAs

ncRNA	Size	Function	Disease
Housekeeping nc-RNA			
rRNA	5S (120 nt), 5.8S (150 nt), 18S (2100 nt) and 28S (5050 nt)	5S RNA- enhance protein synthesis by stabilization of a ribosome structure 5.8S RNA-ribosome translocation 18S RNA-active center of protein synthesis 28S RNA- initiation of polypeptide synthesis in eukaryotes	Defects in ribosome structure and function, disruption of the cardiac protein balance and induction of cardiac hypertrophy are caused by abnormal pre-rRNA processing[1,53,61].
tRNA	~73-95 nt	Protein synthesis, stress response programs, amino acid and porphyrine metabolism, apoptosis and cell signaling	Mutations in tRNA genes or genes that control tRNA biogenesis or function, which are frequently congenital and degenerative in nature and tRF that prevents tumor metastasis[5,19,36].
SnRNA	150 nt	Processing of pre-messenger RNA in the nucleus, regulation of transcription factors, maintaining the telomeres	Mutations in SnRNA leads to spinal muscular atrophy, dyskeratosis congenita, Prader-Willi syndrome, Medulloblastoma[17,25].
SnoRNA	60-300 nt	Regulate stability of a set of protein-coding mRNAs	Lung cancer, asthma, chronic obstructive pulmonary disease and pulmonary hypertension are all advanced by abnormal snoRNA expression. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) cells exhibit under expression[57].
Regulatory ncRNA-Short nc-RNA (less than 200 nt)			
MiRNA	19-25 nt	mRNA stability, immune responses, aging, cholesterol metabolism, insulin secretion, neurogenesis, cardiac and skeletal muscle development, hematopoiesis, stem cell differentiation, developmental processes, apoptosis and cell-cycle control	The development of Diamond-Blackfan anemia and myelodysplastic syndrome (MDS) is associated with deregulation of miRNAs, miR-502-3p to be implicated in other human diseases such as osteoporosis, diabetes, muscular dystrophy, tuberculosis, multiple cancers and neurodegenerative disorders[3,39,43].
SiRNA	20-24 nt	Controlling vital processes such as cell growth, tissue differentiation, heterochromatin formation and cell proliferation	Dysfunction is linked to cardiovascular disease, neurological disorders and many types of cancer[14].
PiRNA	24-30nt	Development and maintenance of germ line by silencing the transposons and protect the integrity of the genome	Regulate both cancer and cardiovascular disease in an mTOR-dependent manner[11].
scaRNA	144 nt	Modifications of other RNAs, including rRNAs, snRNAs, mRNAs and tRNAs	Congenital heart anomalies, neuromuscular disorders and various malignancies[49].
Regulatory ncRNA-Long nc-RNA (more than 200 nucleotides)			
lincRNA	~90-5100 nt	Modify nuclear architecture and sequester intracellular molecules to fine-tune gene expression. They also play a role in the regulation of chromatin topology.	Neurodegenerative diseases, associated with nucleolar stress and reduced rRNA production[40].
cirRNA	100 nt to > 4 kb	Open reading frames and the initiation codon AUG are linked to polysomes.	Prevents atherosclerosis by limiting rRNA maturation and ribosome biogenesis to stop the growth of vascular smooth muscle cells[56].
eRNA	0.1-9 Kb nt	Act as scaffolds to maintain transcriptional complexes by directly influencing target genes, long-range chromatin interactions and markers for active enhancers in the local enhancer-promoter loop.	Tumorigenesis is aided by aberrant signaling pathways and oncogene activation, cardiovascular and in neurodegenerative diseases[15.54].
NAT	>200 nt	Gene expression regulation, from controlling epigenetic modifications to modulating post-transcriptional modifications	Etiology of human disorders such as cancers and neurodegenerative and cardiovascular diseases[8].

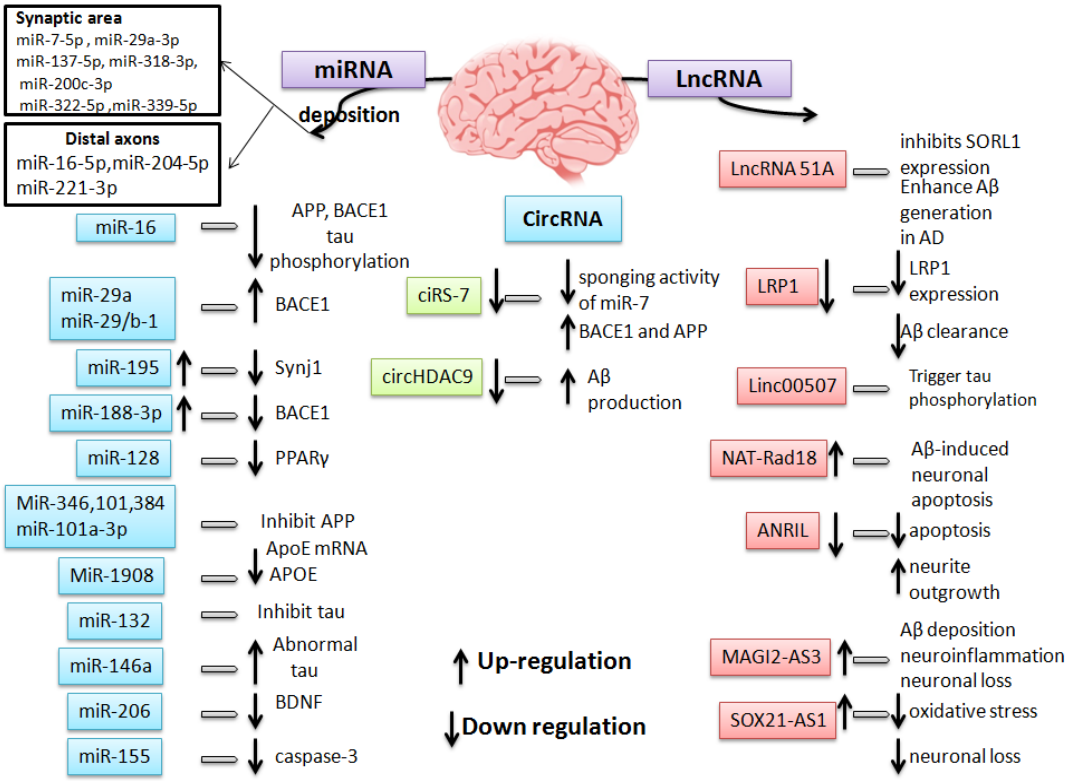

Figure 3: Impact of various non-coding RNAs in pathogenesis of Alzheimers Disease

In neuronal cell lines, miR 16 controls the expression of APP, BACE1 and nicastrin, which affects the total amount of tau phosphorylation. MiR 29a/b 1 decrease correlates with elevated BACE1 levels in a cluster of AMD subjects. Overexpression of miR 195 in ApoE4 mouse models rescues cognitive deficits and reduces amyloid burden, indicating therapeutic potential. MiR 188 3p over expression suppresses BACE1 gene transcription, reducing Aβ production in transgenic mice.[10]

MiRNAs also affect Aβ clearance, with miR 1908 interacting with ApoE mRNA, diminishing ApoE-mediated Aβ clearance in AMD patients.[55] MiR 33 suppresses ABCA1 expression, increasing extracellular Aβ accumulation and presenting a potential target for AMD treatment.[27] MiR 512 inhibits anti-apoptotic proteins MCL1 and cFLIP, with reduced levels associated with tau hyper-phosphorylation in AMD brains. MiR 137 inhibits tau hyper-phosphorylation by targeting CACNA1C mRNA in the hippocampus and cortex of AMD mice.[24] MiR 206, which is unregulated in AMD patients' serum and reduces BDNF expression by binding to the 3′ UTR of BDNF mRNA, has an impact on BDNF levels, which are known to drop in AMD patients.[58]

Significantly reduced in AMD patients, miR 133b demonstrates neuroprotective properties by reducing Aβ-induced neuronal apoptosis and raising the possibility that it could be a biomarker.[59] Pro-inflammatory cytokines are correlated with elevated levels of miR 155 in AMD rats. Rats' learning and memory are improved by miR 155 knockdown which also inhibits caspase 3 levels and inflammatory signalling pathways. In AMD, neuroinflammation is linked to miR 132 and miR 212.[20]

Oxidative stress, a contributor to AMD pathogenesis, is linked to abnormal expression of miR 34a, miR 34c and miR 98, leading to Aβ deposition in the hippocampus.[23] Reactive oxygen species up regulate miR 20a, which reduces Aβ formation and accumulation by inhibiting APP mRNA transcription, indicating a protective role for the miRNA.[60] Fig. 3 illustrates the regulatory mechanisms of various miRNAs in AMD pathogenesis.

Age-related neurodegenerative diseases, such as AMD, can be brought on by the accumulation of circular RNAs (CircRNAs) which are expressed in the central nervous system (CNS) and tend to accumulate during the normal aging process of the brain. CircRNAs are positioned as possible therapeutic targets and biomarkers for AMD diagnosis and treatment as a result of this susceptibility.[29] In mammalian cells, circRNAs function as microRNA sponges, participating in pathogenic processes associated with various human diseases including neurological disorders.[45]

CiRS-7 is one well-researched circRNA associated with AMD. This RNA attaches itself to the abundantly found well-preserved miRNA-7 in the human brain. Because CiRS-7 has particular binding sites for miRNA-7, it functions as a "sponge" to inhibit miRNA-7.[21] ciRS-7 is down regulated in AMD patients' hippocampi which lowers

its activity as a miRNA-7 sponge and raises endogenous levels of miRNA-7 in AMD.[33] The brain of an AMD patient has an autophagic mechanism for clearing amyloid peptides and this process is aided by the down-regulation of UBE2A and up-regulation of miRNA-7 targets.[32] Fig. 3 provides impact of various circRNA in AMD.

Piwi-interacting RNAs (piRNAs) exhibit heightened expression in neurodegenerative diseases, as evidenced by their over expression in a study involving AMD patients.[22] 9,453piRNAs were found in the brains of AMD patients by Qiu et al[41] investigation. 103piRNAs were associated with an increased risk of AMD of which 22 were down regulated and 81 were up regulated. PiRNAs have the potential to be AMD biomarkers due to their association with genome-wide significant SNPs like ApoE.[41] Another study by Roy et al[44] found 146 up regulated piRNAs in AMD patients and the results showed correlations with five important targets of the AMD-related pathway, which are regulated by piR-38240, piR-34393, piR-40666 and piR-51810 and which include the genes CYCS, LIN7C, KPNA6 and RAB11A.

Ten differentially expressed piRNAs including piR-hsa-1282, piR-hsa-23538, piR-hsa-23566, piR-hsa-27400, piR-hsa-27725, piR-hsa-28116, piR-hsa-28189, piR-hsa-28390, piR-hsa-29114 and piR-hsa-7193, were found by analysis of two AMD datasets.[44] Many long non-coding RNAs (lncRNAs) have important roles in the pathophysiology of AMD. These include BACE1 AS, MALAT1, 51A, 17A, NDM29, BC200, NAT Rad18 and BDNF AS. They also contribute to AMD pathogenesis by regulating tau phosphorylation, APP processing, synaptic plasticity and neuroinflammation.[12]

In both the blood and brain of AMD patients as well as in AMD animal models, BACE1 AS, which is transcribed from the sense strand of the BACE1 gene, shows high expression. Its knockdown enhances memory and learning in AMD mice, lowers BACE1 and Aβ levels and prevents tau phosphorylation in the hippocampus.[37] Another lncRNA BC200 accelerates the progression of AMD by modifying in AMD. Role of miRNA in AMD is given in fig. 3.

Prospects of non-coding RNAs as potential therapeutic targets and biomarkers for AMD: Non-coding RNAs (ncRNAs) have emerged as pivotal contributors within the intricate genetic and epigenetic network influencing the development and progression of AMD. The implication is that ncRNAs can serve roles such as therapeutic targets, utilized for therapeutic benefits, or can function as biomarkers for AMD. A range of FDA-approved ncRNA-based therapies for various diseases has paved the way for ongoing studies aiming to pinpoint viable ncRNA therapeutic targets specific to AMD.

MicroRNAs and long non-coding RNAs are two of the ncRNA families that have been the subject of more research due to their potential as treatment targets for AMD. Based on their inherent contributions to AMD pathophysiology, several highlighted studies indicate that ncRNA manipulation holds promise for delaying the course of the disease and producing positive clinical outcomes. The potential of ncRNAs as therapeutic targets is highlighted by their expression profiles which reflect different pathological processes in the brains of patients with AMD.

Changes in the expression of particular microRNAs at different Braak stages in AMD patients from mild cognitive impairment to clinically severe stages highlight their possible therapeutic utility.[38] Dysregulation of miRNAs influences the course of AMD by controlling target genes and signaling pathways, potentially providing treatment for a variety of neurodegenerative diseases. A novel strategy for miRNA therapeutics is called microRNA mimetic activity which entails turning double-stranded RNA molecules that have been processed *in vivo* into useful microRNAs.

Other miRNA mimics are made based on the complementary sequence of the target miRNA and are intended to block endogenous miRNA functions. The pathophysiology of AMD is also significantly influenced by long non-coding RNAs and efforts are being made to develop therapeutics that specifically target them.

The ability of oligonucleotide compounds, antisense oligonucleotides and small interfering RNAs to target and knockout particular lncRNAs and produce therapeutic effects is being studied. Because circulating ncRNAs exhibit changes in expression throughout the course of the disease, they have the potential to serve as biomarkers for the early detection of AMD in serum or cerebrospinal fluid (CSF). Particular miRNAs and piRNAs have demonstrated promise as diagnostic or prognostic indicators for AMD. McSwiggen et al[35] patented 325 siRNAs that target BACE and significantly reduced BACE expression by 40-90%.

Conclusion

AMD stands out among neurodegenerative diseases, significantly impacting global populations and presenting limited therapeutic options with associated adverse effects. Despite numerous promising outcomes in cellular and animal models, the translation of successful results to human trials remains challenging, owing to the intricate and interconnected pathological mechanisms underlying AMD. Given the prolonged timeline for therapeutic development, an alternative focus on accessible and non-invasive early AMD diagnosis appears crucial. If therapies struggle to meet therapeutic standards promptly, effective pre-clinical AMD diagnosis could potentially alter the disease's trajectory.

Furthermore, the exploration of novel biomarkers holds promise in identifying new target molecules, paving the way for diverse approaches to AMD treatment. In summary, there persists a continual and unmet need for enhanced diagnostic and therapeutic strategies with RNA-based tools demonstrating significant advantages over traditional

methods. From a broader perspective, recent discoveries and studies indicate that we stand on the cusp of a new era in RNA-based diagnostics and therapeutics, suggesting the potential dominance in future biomedical and clinical applications.

Acknowledgement
We thank the Vignan Institute of Pharmaceutical Technology for the facilities and tools provided.

References
1. Abou Elela S. and Nazar R.N., Role of the 5.8S rRNA in ribosome translocation, *Nucleic Acids Research*, **25(9)**, 1788-1794 **(1997)**

2. Aguayo L.G., Oprazo C.R. and Parodi L.R., Real time electrophysiological testing of agents of interest for treatment of amyloid-type diseases, United States Patent **(2013)**

3. Alkhatabi H.A. et al, RPL27A is a target of miR-595 and may contribute to the myelodysplastic phenotype through ribosomal dysgenesis, *Oncotarget*, **7(30)**, 47875-47890, doi: 10.18632/oncotarget.10293 **(2016)**

4. Alzheimer's association report, Alzheimer's disease facts and figures, *Alzheimer's Dement*, **19,** 1598-1695, doi.org/10.1002/alz.13016 **(2023)**

5. Ashleigh E., Schaffer O.P. and Jeffery MColler, TRNA metabolism and neurodevelopmental disorders, *Annual Review of Genomics and Human Genetics*, **20(1)**, 359-387 **(2019)**

6. Bak M. et al, MicroRNA expression in the adult mouse central nervous system, *RNA*, **14**, 432-444 **(2008)**

7. Bartus R.T. and Emerich D.F., Cholinergic markers in Alzheimer disease, *Journal of the American Medical Association*, **282(23)**, 2208-2209 **(1999)**

8. Batista P.J. and Chang H.Y., Long noncoding RNAs: cellular address codes in development and disease, *Cell*, **152(6)**, 1298-1307 **(2013)**

9. Cai Z., Zhou Y., Liu Z., Ke Z. and Zhao B., Autophagy dysfunction upregulates beta-amyloid peptides via enhancing the activity of gamma-secretase complex, *Neuropsychiatric Disease and Treatment*, **11**, 2091-2099 **(2015)**

10. Cao J. et al, MicroRNA-195 rescues ApoE4-induced cognitive deficits and lysosomal defects in Alzheimer's disease pathogenesis, *Molecular Psychiatry*, **26**, 4687-4701 **(2021)**

11. Chong Z.Z., Shang Y.C. and Maiese K., Cardiovascular Disease and mTOR Signaling, *Trends in Cardiovascular Medicine*, **21**, 151-155 **(2011)**

12. Cortini F., Roma F. and Villa C., Emerging roles of long non-coding RNAs in the pathogenesis of Alzheimer's disease, *Ageing Research Reviews*, **50**, 19-26 **(2019)**

13. Cummings J.L., Alzheimer's disease, *The New England Journal of Medicine*, **351(1)**, 56-67 **(2004)**

14. Dana H. et al, Molecular mechanisms and biological functions of siRNA, *International Journal of Biomedical Science*, **13(2)**, 48-57 **(2017)**

15. de Lara J.C.F., Arzate R.G. and Recillas T.F., Enhancer RNAs: Insights into their biological role, *Epigenetics Insights*, **12**, 2516865719846093 **(2019)**

16. Elisabetta L., Konrad D. and Domenico P., The neurobiology of non-coding RNAs and Alzheimer's disease pathogenesis: pathways, mechanisms and translational opportunities, *Ageing Research Reviews*, **71**, doi.org/10.1016/j.arr.2021.101425 **(2021)**

17. Fica S.M. et al, RNA catalyses nuclear pre-mRNA splicing, *Nature*, **503(7475)**, 229-234 **(2013)**

18. Friedman L.G., Qureshi Y.H. and Yu W.H., Promoting autophagic clearance: viable therapeutic targets in Alzheimer's disease, *Neurotherapeutics*, **12(1)**, 94-108 **(2015)**

19. Gong M., Deng Y., Xiang Y. and Dong Y., The role and mechanism of action of tRNA-derived fragments in the diagnosis and treatment of malignant tumors, *Cell Communication Signal*, **21**, 62, doi.org/10.1186/s12964-023-01079-3 **(2023)**

20. Hadar A. et al, SIRT1, miR-132 and miR-212 link human longevity to Alzheimer's Disease, *Scientific Reports*, **8**, 8465 **(2018)**

21. Hansen T.B. et al, Natural RNA circles function as efficient microRNA sponges, *Nature*, **495**, 384-388 **(2013)**

22. Huang X. and Wong G., An old weapon with a new function: PIWI-interacting RNAs in neurodegenerative diseases, *Translational Neurodegeneration*, **10**, 9 **(2021)**

23. Jankowsky J.L. et al, Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: Evidence for augmentation of a 42-specific gamma secretase, *Human Molecular Genetics and Genomics*, **13**, 159-170 **(2004)**

24. Jiang Y. et al, Micro-RNA-137 Inhibits Tau hyperphosphorylation in alzheimer's disease and targets the CACNA1C Gene in transgenic mice and human neuroblastoma SH-SY5Y cells, *Medical Science Monitor*, **24**, 5635-5644 **(2018)**

25. Kaida D., Berg M.G., Younis I., Kasim M., Singh L.N., Wan L. and Dreyfuss G.U., snRNP protects pre-mRNAs from premature cleavage and polyadenylation, *Nature*, **468(7324)**, 664-668 **(2010)**

26. Kasa P., Rakonczay Z. and Gulya K., The cholinergic system in Alzheimer's disease, *Progress in Neurobiology*, **52(6)**, 511-535 **(1997)**

27. Kim J. et al, MicroRNA-33 Regulates ApoE lipidation and amyloid-beta metabolism in the brain, *Journal of Neuroscience*, **35**, 14717-14726 **(2015)**

28. Kunz L. et al, Reduced grid-cell-like representations in adults at genetic risk for Alzheimer's disease, *Science*, **350(6259)**, 430-433 **(2015)**

29. Lam J.K., Chow M.Y., Zhang Y. and Leung S.W., SiRNA Versus miRNA as therapeutics for gene silencing, *Molecular Therapy Nucleic Acids*, **4**, e252 **(2015)**

30. Li J. et al, Differential regulation of amyloid-β endocytic trafficking and lysosomal degradation by apolipoprotein E isoforms, *Journal of Biological Chemistry*, **287(53)**, 44593-44601 **(2012)**

31. Liljegren M., Landqvist W.M., Rydbeck R. and Englund E., Police interactions among neuropathologically confirmed dementia patients: prevalence and cause, *Alzheimer Disease & Associated Disorders*, **32(4)**, 346-350 **(2018)**

32. Lonskaya I., Shekoyan A.R., Hebron M.L., Desforges N., Algarzae N.K. and Moussa C.E., Diminished parkin solubility and co-localization with intraneuronal amyloid-β are associated with autophagic defects in Alzheimer's disease, *Journal of Alzheimer's Disease*, **33**, 231-247 **(2013)**

33. Lukiw W.J., Circular RNA (circRNA) in Alzheimer's Disease (AD), *Frontiers in Genetics*, **4**, 307 **(2013)**

34. Lunardi P.S., Effect of Huperzine-A on secretion of S100B in primary culture of astrocytes and hippocampal slices, Thesis, 44 **(2010)**

35. McSwiggen J. and Beigelman L., RNA interference mediated treatment of Alzheimer's disease using short interfering nucleic Acid (SINA) US20100168208, US Patent **(2010)**

36. Medha R. and Ibba M., TRNAs as regulators of biological processes, *Frontiers in Genetics*, **5**, 171 **(2014)**

37. Modarresi F., Faghihi M.A., Patel N.S., Sahagan B.G., Wahlestedt C. and Lopez-Toledano M.A., Knockdown of BACE1-AS nonprotein-coding transcript modulates Beta-Amyloid-related hippocampal neurogenesis, *International Journal of Alzheimer's Disease*, 2011929042 **(2011)**

38. Mus E., Hof P.R. and Tiedge H., Dendritic BC200 RNA in aging and in Alzheimer's disease, The Proceedings of the National Academy of Sciences USA, **104**, 10679-10684 **(2007)**

39. Ning M.S., Kim A.S., Prasad N., Levy S.E., Zhang H. and Andl T., Characterization of the Merkel cell carcinoma miRNome, *Journal of Skin Cancer*, **2014**, 289548 **(2014)**

40. Pietrzak M., Rempala G., Nelson P.T. and Zheng J.J., Hetman M. Epigenetic silencing of nucleolar rRNA genes in Alzheimer's disease, *PLoS ONE*, **6**, e22585 **(2011)**

41. Qiu W. et al, Transcriptome-wide piRNA profiling in human brains of Alzheimer's disease, *Neurobiology of Aging*, **57**, 170-177 **(2017)**

42. Radhakrishnan B. and Alwin P.A.A., Role of miRNA-9 in Brain Development, *Journal of Experimental Neuroscience*, **10**, 101-120 **(2016)**

43. Rivera J., Gangwani L. and Kumar S., Mitochondria localized microRNAs: An unexplored miRNA niche in alzheimer's disease and aging, *Cells*, **12**, 742 **(2023)**

44. Roy J., Sarkar A., Parida S., Ghosh Z. and Mallick B., Small RNA sequencing revealed dysregulated piRNAs in Alzheimer's Disease and their probable role in pathogenesis, *Molecular BioSystems*, **13,** 565-576 **(2017)**

45. Shao Y. and Chen Y., Roles of circular RNAs in neurologic disease, *Frontiers in Molecular Neuroscience*, **9**, 25 **(2016)**

46. Shenoy A., Danial M. and Blelloch R.H., Let-7 and miR-125 cooperate to prime progenitors for astrogliogenesis, *EMBO Journal*, **34**, 1180-1194 **(2015)**

47. Stancu I.C., Vasconcelos B., Terwel D. and Dewachter I., Models of β-amyloid induced Tau-pathology: the long and folded road to understand the mechanism, *Molecular Neurodegeneration*, **9**, 51 **(2014)**

48. Szymanski M., Barciszewska M.Z., Erdmann V.A. and Barciszewski J., 5S Ribosomal RNA Database, *Nucleic Acids Research*, **30(1)**, 176-178, doi:10.1093/nar/30.1.176 **(2002)**

49. Thuy C. et al, Biology and clinical relevance of noncoding sno/ scaRNAs, *Trends in Cardiovascular Medicine*, **28(2)**, 81-90, doi.org/10.1016/j.tcm.2017.08.002 **(2018)**

50. Tong B.C., Wu A.J., Li M. and Cheung K.H., Calcium signaling in alzheimer's disease & therapies, *Biochimica et Biophysica Acta - Molecular Cell Research*, **1865(11 Pt B)**, 1745-1760 **(2018)**

51. Varghese Lijo N., Schwenke Daryl O. and Katare Rajesh, Role of noncoding RNAs in cardiac ageing, *Frontiers in Cardiovascular Medicine*, doi:10.3389/fcvm.2023.1142575 **(2023)**

52. Vik-Mo A.O., Bencze J., Ballard C., Hortobágyi T. and Aarsland D., Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease, *Journal of Neurology, Neurosurgery and Psychiatry*, **90(6)**, 728-730 **(2019)**

53. Wallace L., Theou O., Rockwood K. and Andrew M.K., Relationship between frailty and Alzheimer's disease biomarkers: A scoping review, *Alzheimer's and Dementia (Amsterdam)*, **10**, 394-401 **(2018)**

54. Wan L., Li W., Meng Y., Hou Y., Chen M. and Xu B., Inflammatory Immune-Associated eRNA: mechanisms, functions and therapeutic prospects, *Frontiers in Immunology*, **13**, 849451, doi:10.3389/fimmu.2022.849451 **(2022)**

55. Wang Z. et al, The microRNA-1908 up- regulation in the peripheral blood cells impairs amyloid clearance by targeting ApoE, *International Journal of Geriatric Psychiatry*, **33**, 980-986 **(2018)**

56. Wilusz J.E., Circular RNAs: unexpected outputs of many protein-coding genes, *RNA Biology*, **14**, 1007-1017 **(2017)**

57. Xiaoying L., Md Khadem A., Lan Z., Kamal D. and Yuqiang M., The emerging diagnostic and therapeutic roles of small nucleolar RNAs in lung disease, *Biomedicine & Pharmacotherapy*, doi.org/10.1016/j.biopha.2023.114519 **(2023)**

58. Xie B. et al, Serum miR-206 and miR-132 as potential circulating biomarkers for mild cognitive impairment, *Journal of Alzheimer's Disease*, **45**, 721-731 **(2015)**

59. Yang Q., Zhao Q. and Yin Y., MiR-133b is a potential diagnostic biomarker for Alzheimer's disease and has a

neuroprotective role, *Experimental and Therapeutic Medicine*, **18**, 2711-2718 **(2019)**

60. Zhang R. et al, Screening of microRNAs associated with Alzheimer's disease using oxidative stress cell model and different strains of senescence accelerated mice, *Journal of the Neurological Sciences*, **338**, 57-64 **(2014)**

61. Zhang X., Ren Z., Xu W. and Jiang Z., Necroptosis in atherosclerosis, Clinica *Chimica Acta*, **534**, 22-28 **(2022)**

62. Zhang Y. et al, The Role of Non-coding RNAs in Alzheimer's Disease: from regulated mechanism to therapeutic targets and diagnostic biomarkers, *Frontiers in Aging Neuroscience*, **13**, 654978, doi:10.3389/fnagi.2021.654978 **(2021)**

63. Zhong Z. et al, MiR-16 attenuates beta-amyloid-induced neurotoxicity through targeting beta-site amyloid precursor protein-cleaving enzyme 1 in an Alzheimer's disease cell model, *Neuro Report*, **29**, 1365-1372 **(2018)**

64. Zhu L. et al, Phospholipid dysregulation contributes to ApoE4-associated cognitive deficits in Alzheimer's disease pathogenesis, *National Academy of Sciences of the United States of America*, **112(38)**, 11965-11970 **(2015)**.

(Received 25th November 2023, accepted 07th February 2024)