International Journal Of Public Mental Health And Neurosciences
ISSN: 2394-4668
(An Official publication of Sarvasumana Association)

Interactions between long non-coding RNAs and proteins to elucidate the mechanism of neurodegenerative disease onset

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Abstract— Neurodegenerative diseases are progressively becoming the utmost burden to population and characterized by the loss of nerve cells or myelin in the brain and spinal cord, which worsens over time and leads to dysfunction. The role of long non- coding RNAs (lncRNAs) in neurodegeneration is a fascinating area of research that has gained significant attention in recent years. Currently, lncRNAs are a valuable area of potential research. Long non-coding RNAs (lncRNAs) are non-protein or low-protein coding transcripts containing more than 200 nucleotides in eukaryotic cells. They represent an important part of the cell's transcriptional output and exhibit functional properties, viz. tissue-specific expression, cell fate determination, controlled expression, RNA processing and editing etc. lncRNAs are involved in disease pathogenesis through a variety of mechanisms such as decoys, scaffolds, miRNA sequestrator, histone modifiers, and transcriptional interference and highly heterogeneous and exhibit multifaceted biological functions and interact with many other proteins. The pathological modifications of neurodegenerative diseases are related to mitochondrial dysfunction, oxidative stress, and inflammation, which further stimulate the progression of neurodegenerative diseases.

Detailed knowledge of the roles of ncRNAs may help in their further use as novel biomarkers for therapeutic aspects. Long non-coding RNAs (lncRNAs) have gathered significant attention for their involvement in neurodegenerative diseases, primarily through their protein-binding capabilities. These interactions can influence gene expression, protein homeostasis, and cellular stress responses, which are crucial in the pathogenesis of these diseases. This work aims to highlight the protein binding interaction between the lncRNA and neurodegenerative diseases. Specifically, we focus on how the protein binding interaction in the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are involved to excite the progression of neurodegenerative diseases with the help of lncRNA regulation.

Index Terms— Neurodegenerative diseases (NDDs), long non-coding RNAs (lncRNAs), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), protein binding interaction.

I. INTRODUCTION

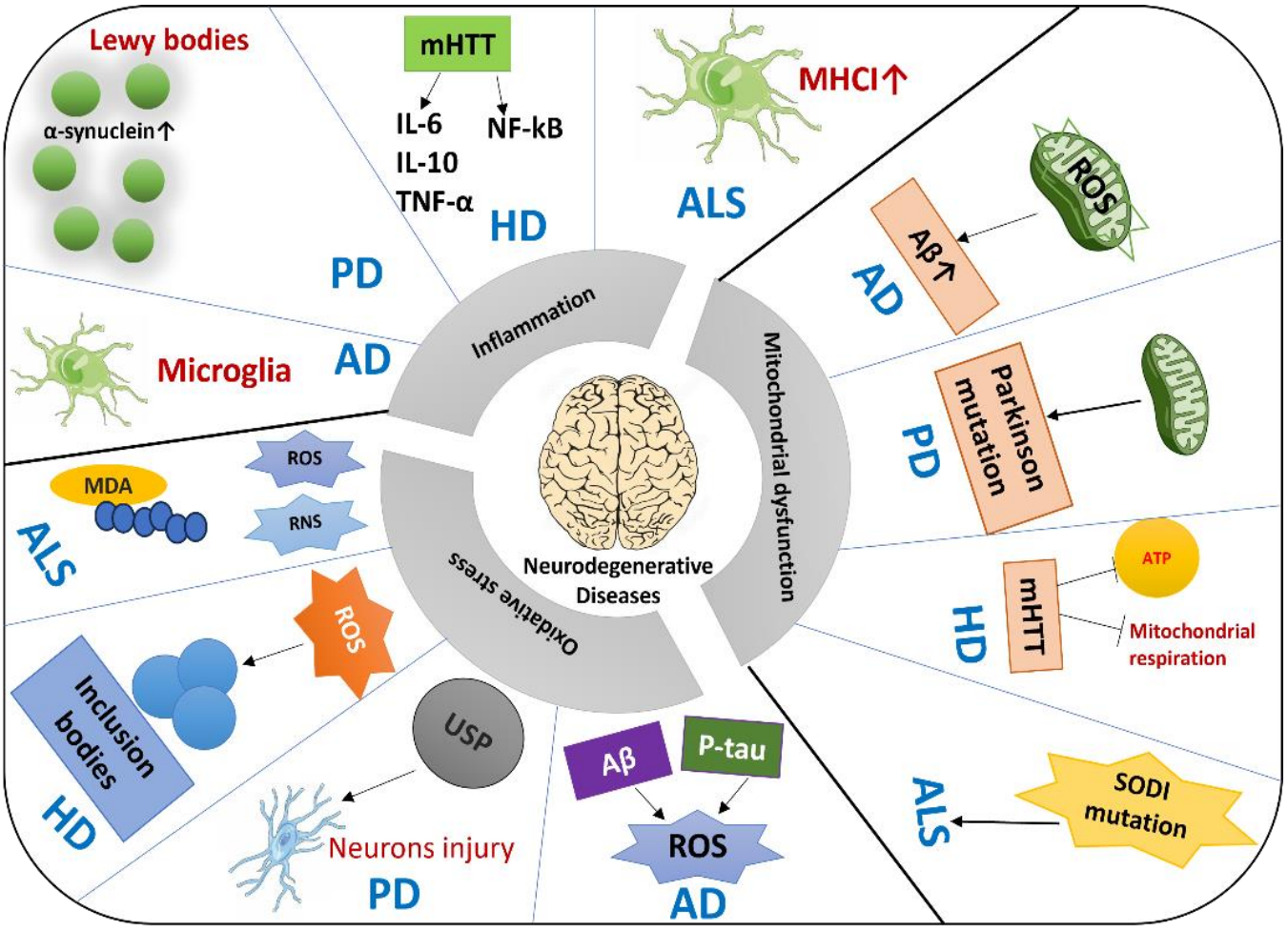
Less than 2% of transcripts encode proteins, and the remaining 98–99% are noncoding RNAs (ncRNAs) in the human genome. Based on their length, ncRNAs are classified into small non-coding transcripts such as miRNA, snRNA, piwi RNA [1,2] and long non-coding RNA (lncRNA) (transcripts with more than 200 nucleotides) [3]. Long ncRNAs (ncRNAs) are RNA transcripts larger than 200 nucleotides (nt) in length without a canonical open reading frame. GENCODE studies in humans revealed that there are more than 19,000 lncRNAs encoded in mammalian cells and some of them appear to play essential roles in many neurological processes such as neurogenesis, metabolism, proliferation, aging, and apoptosis in the central nervous system [4,5,6,7,8,9]. Some key characteristics of lncRNA include poor sequence conservation in the hierarchy and the sequence has fewer exons. ncRNAs can be poly-adenylated or not, and these molecules mainly rely on secondary structure to perform their function, and the expression pattern of ncRNAs is tissue-specific [10]. lncRNA is transcribed by RNA polymerase II, 5-cap, spliced, and has promoter regions. Most of them, are also polyadenylated at the 3-terminus [11]. The importance of ncRNAs as key regulators in the development, progression, including altering gene expression by modulating chromatin structure and regulating transcription, post-transcriptional modification and manifestation of metabolic diseases [12]. These lncRNAs have several different functions, however they may all be generically categorized as transcriptional interferers, scaffolds, mi-RNA sequestrators, decoys, and histone regulators. [13,14]. lncRNA may work in the following modes. (a) Through chromatin interaction, lncRNA controls the expression of associated genes by influencing chromatin remodeling and histone modification in the upstream promoter regions of coding genes. (b) By Interacting with proteins, lncRNA can be used as a guiding molecule for a single protein or it can act as a scaffold molecule for two or more proteins to create a protein complex, which is subsequently recruited to specific sites in coding genes to control the expression of genes downstream. Furthermore,

lncRNA can be employed as a protein bait molecule. It has the ability to move proteins attached to the genome and alter their intracellular location, blocking the transcription and expression of genes. (c) By Interaction with other RNAs, many specific microRNA (miRNA) recognition sites are present in lncRNA. Depending on their subcellular location in the nucleus or cytoplasm, lncRNAs can interfere with many transcriptional and post-transcriptional genetic regulations by recruiting or inhibiting transcription factors [15,16], alternative splicing [17], as well as mRNA translation. Cytoplasmic lncRNA repeatedly interacts with miRNAs to act as molecular scaffolds for RNA-protein complexes [18,19]. A general mechanism of neurodegenerative diseases has been shown in Figure, which causes dysfunction in Central nervous system.

Fig. General mechanisms of neurodegenerative diseases. (1) Aβ deposition occurs through reactive oxygen species (ROS) production in AD, Parkinson mutations occur in PD, whereas the cause of ALS is SOD1 mutation are caused due to mitochondria dysfunction. (2) By cause of oxidative stress/imbalance, the production of Aβ and p-Tau occurs in AD. In Parkinson's disease (PD), it leads to UPS dysfunction, which exacerbates dopaminergic neuronal damage. In ALS, it also results in an excess of reactive oxygen and nitrogen species in addition to MDA. (3) Microglia regulate inflammation throughout the innate response of the CNS in AD. The development of Parkinson's disease is linked to the accumulation and aggregation of α-synuclein in Lewy bodies. The microgliosis growth can result in a decline in the level of MHC-I, which contributes to ALS progression [20].

AD= Alzheimer's Disease; PD= Parkinson's Disease; ALS= Amyotrophic Lateral Sclerosis; Aβ= Amyloid-β peptide; SOD= Superoxide Dismutase; p-Tau= hyperphosphorylated tau; UPS= Ubiquitin-proteasome System; MHC= Major Histocompatibility Complex class-I; MDA= Malondialdehyde.

lncRNAs relative to protein coding genes, based on genome location can be divided into five categories (Table): (A) long intergenic non-coding RNAs (LincRNAs), comprising of independent transcriptional units located between protein codes; (B) bidirectional lncRNAs transcribed from different bidirectional promoters ;(C) intron transcripts in the intron region of protein coding genes; (D) Sense lncRNAs transcribed by the sense chain of the protein-coding gene overlaps with at least one exon of the protein-coding gene on the same chain has



the same transcriptional direction. The sense lncRNAs may partially overlap with the protein coding gene, or it may cover the complete sequence of the protein coding gene; (E) Antisense lncRNAs transcribed by a complementary DNA chain of protein-encoded genes, transcribed in the opposite direction and overlaps with at least one exon of the positive gene [21]. The pathology of neurodegenerative diseases is linked to accumulation of certain proteins and lncRNAs are associated with different protein aggregation events and disease pathogenesis. Some of the well-known hallmarks of neurodegenerative diseases are mutant huntingtin (mHTT) aggregates in Huntington's disease (HD) [22], α-synuclein-associated Lewy bodies in Parkinson's disease (PD), Amyloid-β aggregation and hyperphosphorylated Tau in Alzheimer's disease (AD), and TDP43 proteinopathies in frontotemporal lobe dementia (FTLD) and amyotrophic lateral sclerosis (ALS) [23].

Table: Long-non coding RNAs (lncRNAs) classification

Sl.no	Classification of lncRNAs	Examples
A	Intergenic	NEAT1, XIST
B	Bidirectional	HOTAIRM1, Hoxa11as
C	Intronic	Lnc-OR51B4-3
D	Sense	SNHG4
E	Antisense	BACE1-AS, MALAT1

II. LncRNA correlation with protein aggregation in Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder in the common form of dementia and characterized by progressive degeneration of cortical neurons, leading to brain tissue atrophy and clinical symptoms such as dementia and cognitive decline. The two main hallmark characteristics of AD are the accumulation of amyloid-beta (Aβ) in the extracellular senile plaques and hyperphosphorylated tau protein in the intracellular neurofibrillary tangles [24]. Even so, many other factors may cause neurodegeneration, such as neuroinflammation and oxidative stress. Aβ is a polypeptide (contains 39–43 amino acids) produced by proteolysis of the amyloid precursor protein (APP) via β- and γ-secretases [25]. The main cause of neuronal degeneration and cell death in AD brains is the polypeptide [26]. APP is a transmembrane protein that produces Aβ by sequential division of β-site APP cleaving enzyme-1 (BACE1, a membrane-bound aspartic protease) and γ-secretase [27]. The amyloid plaques cause AD in brain disrupt the balanced ratio of Aβ42/Aβ40 [28].

lncRNA BACE1-AS (BACE1-antisense), the antisense transcript of BACE1 transcribed by RNA polymerase II from the antisense strand of the BACE1 locus located on chromosome 11 [29]. It has been observed that BACE1-AS is highly expressed in brains of the AD patients which regulates the expression of BACE1 mRNA, thereby promoting the synthesis of BACE1 protein and further increases the production of Aβ [30]. Elevated BACE1-AS levels in patients with AD, thus suggests that BACE1-AS levels may serve as a potential diagnostic biomarker and therapeutic target for AD [31].

Brain cytoplasmic 200 RNA (BC200 RNA), cytoplasmic lncRNA, mainly expressed in neurons and can be transported to dendrites. BC200 RNA are lncRNA transcripts that are transported as ribonucleoprotein particles to the dendritic processes and bind to poly(A)-binding protein (PABP1), a translational modulator that selectively targets the somatic dendrite domain of neurons [32] and associated with abnormal protein localization by interacting with RNA-binding proteins [33]. Upregulation of BC200 in AD and the aging brain may cause synaptic/dendritic degeneration. BC-200 level also found higher in AD-affected brain region (Brodmann area 9) in Alzheimer's patients compared to the healthy individuals [34]. demonstrated that BC200 RNA expression was distinctly increased in AD brains and specified that higher BC200 levels was paralleled with the severity of AD. Furthermore, BC200 upregulation directly promotes BACE1 level and impair cell feasibility subsequently, thus increases Aβ42 expression [35].

lncRNA Brain cytoplasmic 1 (BC1) comprises a 5' stem-loop domain, followed by a single-stranded central homopolymer A-rich region and a 3' -stem-loop domain [36]. BC1, a translational repressor, modulated by the adjacent A-rich region and 3' stem-loop through interactions with poly(A)- binding protein (PABP), eukaryotic initiation factor 4A (eIF4A), and eIF4B [37]. Additionally, it is abundant in the synapse and hinders translation at initiation. BC1, a cytoplasmic lncRNA in neurons that induces APP mRNA translation through the interaction with the fragile X syndrome protein (FMRP) [38]. Additionally, it has been demonstrated that BC1 inhibition block Aβ from accumulation and aggregation in AD. In comparison, exogenous overexpression of BC1 give rise to Aβ peptides aggregation and induced learning and memory disorders.

A novel ncRNA-17A, synthesized by RNA polymerase III is positioned in the human G-protein-coupled receptor 51 genes (GPR51, GABA B2 receptor) at intron 3 plays role in controlling the alternative splicing of GPR51 which decreases the transcription of GABAB R2 and significantly impairs the GABAB signaling pathway. LncRNA 17A can damage gamma-aminobutyric acid type B (GABAB) signal transduction by generating non-functional receptor isoforms, thus enhance the Aβ42/Aβ40 peptide ratio and promote neurodegeneration [39]. Inflammation in AD brains can trigger

17A expression, thereby enhance the secretion of amyloid-β (Aβ) and increase the inflammation in AD brains [40].
The lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) consists of two subtype transcripts: (1.) NEAT1v1 and (2.) NEAT1v2, which are essential components of para-nuclear plaque formation [41]. Earlier studies have shown that NEAT1 is involved in the manifestation of AD. found that NEAT1 aggravated P-tau (hyperphosphorylated tau protein) expression, Aβ level, and neuron damage via sponging miR107, thus boosting AD progression.
The long non-coding RNA NAT-Rad18, up-regulated in Alzheimer's and post transcriptionally controls the Rad-18 protein, involved in proliferating cell nuclear antigen (PCNA) ubiquitination, DNA repair, nerve damage and increase the susceptibility to neuronal apoptosis and cell death [42].
LncRNA MEG3, an imprinted gene mapped (human chromosome 14 and mouse chromosome 12). It has been demonstrated that upregulation of MEG3 can protect neurons by phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, decrease Aβ expression and lower inflammation injury and damage[43].

lncRNA 51A, antisense transcript of intron 1 of sorting protein-related receptor 1 (SORL1) gene. SORL1 gene interact with APP, affect transport and proteolysis, and participate in AD pathogenesis [44]. Overexpression of 51A promotes Aβ formation by decreasing SORL1 variant A, thereby increase the susceptibility to AD [45].
lncRNA-linc-00507 expression, remarkably upregulated in hippocampus and cerebral cortex which can regulate the expression of microtubule-associated proteins Tau (MAPT) and tau-tubulin protein kinase 1 (TTBK1) via two mechanisms: (1.) as (ceRNA) competitive endogenous RNA to bind with miR181c-5p; (2.) as an enhancer of tau hyperphosphorylation protein by initiating P25/P35 /GSK3β signaling pathway cascade [46].
lncRNA Neuroblastoma differentiation marker 29 (NDM29), transcribed by RNA polymerase III enhances the APP level, which in order increases the generation of two key Aβ isoforms [47]. LncRNA NDM29 also promote the APP synthesis and accelerate the cleavage through γ-secretase and BACE1, which can be restrained by anti-inflammatory agents and accelerated by inflammatory stimulation [48].
Low-density lipoprotein receptor (LDLR)-related protein (LRP1) is a large endo-phagocytic and signal transduction receptor in the LDLR gene family. Apolipoprotein E (ApoE), the ligand of LRP1, involved in senile plaques in AD brains [49], involving a role for LRP1 in the accumulation of Aβ. LRP1-antisense (LRP1-AS) negatively facilitates LRP1 expression at both protein and RNA levels. It was conveyed that LRP1-AS expression was significantly increased in the AD brain [50].

III. LncRNA correlation with protein aggregation in Parkinson's disease (PD)

PD, a common neurodegenerative disorder caused by degeneration of dopaminergic neurons in the substantia nigra-striatum of the midbrain, which decreases dopamine secretion, resulting in a series of extrapyramidal responses, impairments of motor abilities and an abnormal postural gait. The two hallmarks feature of PD include loss of dopaminergic neurons in the substantia nigra and α-synuclein (a presynaptic neuron protein) aggregation in Lewy bodies [51]. Numerous PD-related genes have been identified, including α-synuclein, Parkin, LRRK2 (leucine-rich repeat kinase 2), PINK1 (phosphatase and tensin homologue-induced putative kinase 1), and DJ-1 (also referred as Parkinson disease protein 7 (PARK7)). These genes are known to be associated with mitochondrial function, suggesting the homeostasis properties of mitochondria play a significant role in the disease [52].

A nuclear-enriched lncRNA antisense ubiquitin carboxy-terminal hydrolase L1 (AS-UchL1) has been found to increase the expression of UchL1 protein, that is closely related to brain function and neurodegenerative diseases, at post-transcriptional level depending on a 5r overlapping sequence and an embedded inverted SINEB2 sequence [53]. In neurochemical models of Parkinson's Disease, as a component of Nurr-1 dependent gene network, down-regulated AS-Uch1 results in reduced translation of UchL1 protein. This leads to subsequently inhibition of ubiquitin-proteasome system [54]. The presence of a 5′ overlapping sequence and an embedded inverted short interspersed nuclear elements B2 (SINEB2) element are required for AS-Uchl1 activity. Stress signaling pathways regulate AS Uchl1 function because rapamycin-induced mTORC1 inhibition raises UCHL1 protein levels, which are associated to the transfer of AS Uchl1 RNA from the nucleus to the cytoplasm [55].

The lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) (also called as nuclear-enriched abundant transcript 2 (NEAT2) is highly expressed in neurons and upregulates α-synuclein production when overexpressed [56]. Targeting MALAT1 with β-asarone (the major ingredient of Acorus tatarinowii Schott) reduces its level and therefore serve as a potential therapeutic target for PD [57].

lncRNA Hox transcript antisense intergenic RNA HOTAIR, approximately 2.2 kb lncRNA transcribed from the HOXC locus which is found to be upregulated, furthered PD through an increase in ROS generation and neuroinflammation; therefore, inducing neuronal injury. HOTAIR regulate the autophagy protein ATG10, which may potentially exacerbate the neuronal damage. With HOTAIR, the expression of the protein is enhanced and serves as a sponge for miR-874-5p [58].

LncRNA NEAT1 is also referred to PD progression. The stability of PINK1 protein was enhanced by overexpression of NEAT1, which had a positive correlation with MPTP levels [59]. Mechanistically, via stabilizing PINK1 protein and inhibiting PINK1 protein degradation, NEAT1 positively controlled PINK1 level. In addition, showed that NEAT1 could promote α-synuclein-related apoptosis in PD [60].

In Hungarian PD patients, reports of the lncRNAs UchL1-AS, PINK1-AS, HAR1A, Sox2OT, BCYRN1, ANRIL have been made. They have an impact on transcription factors like HNF4A's binding affinity, which may lead to aberrant expression of target genes like BCYRN1 [61].

IV. LncRNA correlation with protein aggregation in Huntington's disease (HD)

Huntington's disease (HD), also known as chorea or Huntington's chorea, is a rare autosomal dominant neurodegenerative disease characterized by mental decline and loss of neurons in the striatum and cerebral cortex [62]. Polyglutamine is encoded by a CAG repeat sequence located in the first exon of the Huntingtin (HTT) protein. HD is caused by an abnormal expansion of CAG triplet repeat stretch (i.e. trinucleotide) in the first exon of the huntingtin gene, which results in a mutant form of the huntingtin protein containing the expanded polyglutamine region. The mutant HT protein induces neurodegeneration through a variety of mechanisms such as transcriptional disorders, clearance of misfolded proteins, toxic N-terminal fragments, mitochondrial dysfunction and oxidative stress [63].

lncRNA HttAS_v1, an antisense transcript of the Htt gene is expressed at a low levels of HD patients in the frontal cortex of brain. This results in increased expression of Htt mRNA, which in turn drives HD pathogenesis. The transcriptional repressor RE1 silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) is subjected to modulate by Htt through its nuclear translocation. Mutant Htt promotes abnormal nuclear-cytoplasmic transport of REST/NRSF and then leads to abnormal expression of REST target genes, including protein-coding and non-coding genes [64].

MEG3 is also identified as gene trap locus 2 (Gtl2). Numerous aging-related neurodegenerative disorders are regulated by the lncRNA MEG3. Inactivation of Meg3 results in a marked increase in microvascular formation and angiogenesis-promoting gene expressions in the brain [65]. MEG3 is another target of REST and is associated with PRC2 complex [66]. It has been discovered that endogenous Tp53 levels were downregulated and mHTT aggregates were significantly decreased in HD cell models following MEG3 knockout. [67].

Taurine-upregulated gene 1 (TUG1) is actively involved in numerous physiological processes, including modulating genes at epigenetics, transcription, post-transcription, translation, and post-translation [68]. Research has indicated that among lncRNAs relevant to HD, TUG1 is tightly connected with PRC2. Since the altered expression of TUG1 is associated with several biochemical pathways in the HD brain, it is likely due to the involvement of the PRC2 epigenetic regulatory complex.

LncRNA DiGeorge syndrome critical region gene 5 (DGCR5) is regulated by REST in neurodegeneration, is sometimes referred to as linc00037 [69]. The downregulation of DGCR5 in HD brain implies that DGCR5 is closely associated with transcriptional regulation in the progression of HD [70].

Brain-derived neurotrophic factor (BDNF) produces an antisense transcription product called BDNFOS, which increases BDNF transcription and BDNF-mRNA translation in HD. Small interfering RNA (siRNA) treatment with BDNFOS can induce Htt expression. BDNFOS has a protective effect on neurons and improves the HD phenotype, which is of some positive significance in the prevention and treatment of HD [71].

NEAT1 (nuclear paraspeckle assembly transcript 1), a nuclear enriched non-coding RNA is necessary for the development and upkeep of paraspeckles, which are subnuclear bodies present in mammalian cells. [72].

V. LncRNA correlation with protein aggregation in amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, is a progressive neuromuscular degeneration that primarily affects motor neurons of the somatic nervous system. Sporadic ALS(SALS) accounts for up to 90% of ALS cases and the other 10% have a strong genetic component also called as familial ALS (FALS). Mutations in more than 20 genes contribute to FALS [73]. The pathophysiology of ALS remains incompletely understood, although its hallmark clinical features include bulbar palsy, muscle atrophy, and a progressive worsening of limb weakness and pyramidal tract abnormalities, dysphagia, and respiratory muscle involvement [74]. Approximately 5%–10% of patients with ALS have a family history of the disease, but the genes associated with ALS remain to be fully characterized [75]. Amyotrophic lateral sclerosis leads to serious disability and ultimately death from respiratory failure [76]. RNA-binding proteins that are primarily located in the nucleus and are involved in regulating RNA metabolism are TDP43 (TAR DNA-binding domain protein 43) and FUS/TLS (fused in sarcoma/translated in liposarcoma). Research has demonstrated that in non-SOD1 FALS (familial ALS) and SALS (sporadic ALS), abnormal cytosolic accumulation of FUS/TLS and TDP43 directly causes misfolding of wtSOD1 (wild-type Cu/Zn superoxide dismutase), which means that they constitute common molecular pathogenesis mechanisms of ALS [77].

Mutagenic RNA-binding proteins FUS, C9orf72, and TDP-43 have shown in numerous studies to exhibit abnormal RNA metabolism, which is an intrinsic feature of the pathophysiology of ALS [78]. Paraspeckles are essential elements that play defensive roles in the motor neurons (MNs) cellular stress response. A functional aspect of paraspeckles is their involvement in nucleoplasmic sequestration of RNA and

proteins that directly alters target site expression [79]. The accumulation of paraspeckles in the CNS is a hallmark feature of ALS.

LncRNA NEAT1 (nuclear enriched abundant transcript 1) has inherent roles as a scaffold for paraspeckle formation [80]. NEAT1, primarily expressed in spinal motoneurons during the early stages of ALS and are sequence rich in GpCs, plays a role in the pathophysiology of ALS. The NEAT1 mainly binds to TDP43 in the brain tissue of ALS patients and cultured cells (HeLa and SH-SY5Y) [81]. In the early stages of ALS, accessory spot formation frequency increased significantly. NEAT1 was therefore considered to be the scaffold of RNA-binding proteins in ALS patients' motor neuron nuclei. A more thorough investigation revealed that ALS patients' cortex and the neurons in their anterior horn of the spinal cord were significantly enriched in NEAT1. As a component of Paraspeckles, FUS significantly promotes their stability by regulating the steady-state level of NEAT1 and maintaining the structure of the nucleosome [82].

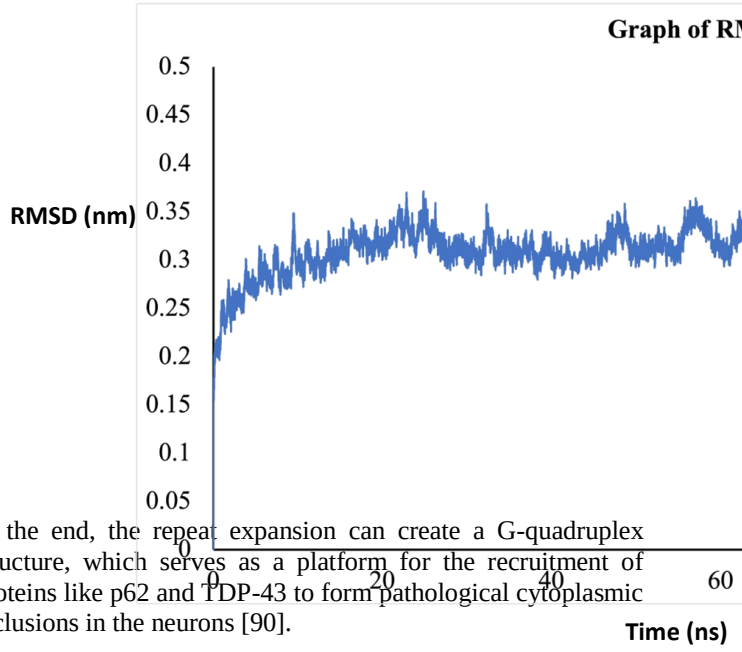
Another long non-coding RNA that is overexpressed in ALS is encoded by Sat III (stress-induced satellite III repeat RNA). Research conducted on functional orthologue in Drosophila melanogaster, Hsrω, revealed that this transcript bound the protein dFUS, which was involved in ALS pathogenesis could also be present in toxic cellular inclusions containing aggregated proteins. Furthermore, Hsrω was also linked to TDP-43 aggregates formation, as it enhanced the expression of the gene encoding for this protein [83].

LncRNA NEAT1_2 was minimally expressed in the motor neurons of healthy people but highly expressed in the motor neurons of people with early-stage ALS, thus suggesting its utility as a biomarker for early ALS diagnostics. In addition, NEAT1_2 may serve as the backbone of RNA and RNA-binding protein (RBP) in the nuclei in ALS motor neurons, thereby regulating the expression of ALS-related RBP and exemplifying the roles of lncRNAs in ALS pathological processes [84]. It has been found that FUS/TLS and TDP43 were enriched in paraspeckles. Besides, it has been investigated markedly raised frequency of para-plaque formation in the early stage of ALS pathology, implying that NEAT1_2 could serve as the scaffold of RBPs in the ALS motor nucleus [85].

Furthermore, TDP-43, an RNA-binding protein involved with ALS, binds to MALAT1 similarly to NEAT1. TDP-43 is noted to be a causative agent of mitochondrial dysfunction with implications in neuroinflammation, a common feature of early-stage ALS. [86].

C9ORF72 is another example of a lncRNA associated with ALS. It regulates autophagy, SG clearance, endocytosis, and interactions with Rab proteins. It reveals a markedly increased number (>30) of GGGGCC repeats between 1a and 2b exons in ALS patient. After this transcript is translated, the protein loses its physiological function, which in healthy conditions, is linked to the regulation of endocytosis and autophagy [87,88].

Moreover, the extended number of hexanucleotide repeats of the sense and antisense RNA can co-localize with proteins involved in SGs formation, which is neurotoxic and leads to neurodegeneration [89].



In the end, the repeat expansion can create a G-quadruplex structure, which serves as a platform for the recruitment of proteins like p62 and TDP-43 to form pathological cytoplasmic inclusions in the neurons [90].

VI. Application of Molecular Modelling Studies in this Context: A Case Study

Molecular modelling is an important procedure to analyze biological data. Thus, to study the interactions between protein and lncRNAs, we need a good three-dimensional structure of the protein-lncRNA complex. However, there are practically no such structures available in the Protein Data Bank. Thus, we chose the following structure as an example:

Crystal structure of human RPP20-RPP25 proteins in complex with the P3 domain of lncRNA RMRP (PDB ID: 6LT7)

The structure contains a 50-mer lncRNA referred to as RMRP which is the RNA component of the mitochondrial RNA-processing endoribonuclease. It was observed that the lncRNA the removal of RMRP by knockdown experiments could induce apoptotic pathways in patients suffering from Alzheimer's Disease [91].

We extracted the structure from the Protein Data Bank using the id 6LT7. We then processed the protein complex in Discovery Studio 2.5 platform with the following parameters:

Forcefield: CHARMm

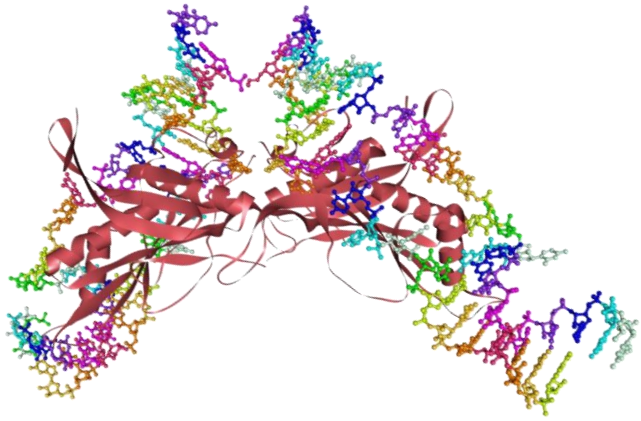
Protocol: Conjugate Gradient with the RMS gradient of energy 0.01 kcal/mol

Our research has revealed crucial insights into the complex interactions between lncRNAs and proteins in neurodegenerative diseases. We will discuss the implications of these findings for future research and potential therapeutic strategies.

We then computed the binding interactions between the lncRNA and the partner proteins. The details of the binding interactions in terms of amino acid residues and nucleic acids are presented in the following tables.

6LT7	Interacting Residues
Chain F: C23, U24, A25, C28, U29, A30, C31, A32, C33, A34, C35, U36, G37, A38, G39, G40, A41, G46, U47, U48, C49, C50, U51, C52, C53, C54, C55, U56, U57, U58, C59, G61, C62	**Chain D:** LEU22, LYS24, ARG25, PRO27, LEU30, TYR38, VAL39, ASN40, LYS42, THR43, PHE45, LYS46, ALA47, ALA50, ARG51, GLN53, GLY54, ARG61, GLU63, ASN64, HIS72, GLY73, LEU74, GLY75, LEU76, ALA77, ARG80, ASN83, GLN87, LEU88, GLY91, THR104, VAL105, LEU107, ARG123, ARG125, ASN126, ASN127, SER128, ALA129, ILE130, HIS131
Chain C: U36	**Chain E:** VAL36, HIS37, ARG39, LYS41, GLU42, GLY43, SER44, LYS45, ILE46, ARG47, ASN48, LEU49, PHE52, ARG72, THR75, LYS76, THR79, GLU82, ILE83, ARG86, ARG87, LYS 130, ASN131

Figure: Structure of the protein-lncRNA complex.



VII. CONCLUSION AND PERSPECTIVES

Knowledge of lncRNAs has grown significantly over the past decade and it is likely that this will continue in the future. lncRNAs have been shown to have diverse molecular functions, such as translation, post-translation, and epigenetic modifications. An in-depth understanding of lncRNA

6LT7	Interacting Residues
Chain C: C23, U24, G27, C28, U29, A30, C31, A32, C33, A34, C35, U36, G37, A38, G39, G46, U47, U48, C49, C50, U51, C52, C53, C54, C55, U56, U57, U58, C59, G61, C62	**Chain A**: GLU19, LEU22, LYS24, ARG25, LEU26, PRO27, LEU30, ARG32, TYR38, VAL39, ASN40, LYS42, THR43, PHE45, LYS46, ALA47, LEU49, ALA50, ARG51, GLN53, GLY54, ARG61, GLU63, ASN64, HIS72, GLY73, LEU74, GLY75, LEU76, ALA77, ARG80, ASN83, GLN87, GLY91, THR104, VAL105, LEU107, ARG123, ARG125, ASN126, ASN127, SER128, ALA129, ILE130, HIS131
Chain F: U36	**Chain B**: VAL36, HIS37, ARG39, LYS41, GLU42, GLY43, SER44, LYS45, ILE46, ARG47, ASN48, LEU49, PHE52, ARG72, THR75, LYS76, THR79, GLU82, ILE83, LYS 130, ASN131

mechanisms and networks from different perspectives will provide new insights into the prevention, diagnosis and treatment of aging-related neurodegenerative diseases. lncRNAs play crucial roles in neurodegenerative diseases (NDDs) through their interactions with proteins, affecting gene expression, protein stability, and cellular responses. These interactions deliver insights into disease mechanisms and possible therapeutic targets. Continued research into lncRNA-protein interactions will hold promise for developing novel strategies to treat neurodegenerative diseases.

VIII. ACKNOWLEDGEMENT

We acknowledge Bioinformatics Infrastructure Facility Center, University of Kalyani, (BT/PR40162/BTIS/137/48/2022, dated 31.10.2022; NNP Project (BT/PR40192/BTIS/137/69/2023, dated 19.12.2023) funded by the Department of Biotechnology (DBT), Govt. of India for the infrastructural support. Special thanks to JIS College of Engineering, Kalyani and Department of BCBP, University of Kalyani for encouraging research and innovation.

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