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Review Article

Non-coding RNAs in the brain: new class of prospective biomarkers and therapeutics

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ABSTRACT

The human genome encrypts around 20,000 protein coding genes, constituting around 1% of the total human genome sequence. The rest of it initially labeled as a "junk DNA" is transcribed to a distinct class of non-coding RNAs (ncRNAs) which do not code for any protein in the cell and their presence was quite intriguing to the researchers. The recent studies, however, have surprisingly revealed the vital roles of these ncRNAs in regulating an array of diverse cellular and biological processes in different organs including brain. The dysfunction of these regulatory ncRNAs in human brain causes certain neurological disorders and brain tumors which earlier have been widely linked to various risk factors such as oxidative stress, genetic mutations, aberrant protein degradation and dysfunctional neural network. This review provides an overview of different types of ncRNAs, their regulatory roles in brain functions and neurological disorders along with their prospects to be used as potential biomarkers and therapeutics.

Keywords: Noncoding RNA, Antisense oligonuclotides, Gene silencing, RNA interference, Gene regulation, RNA sponge, Neurological disorders, Biomarkers, Therapeutics

INTRODUCTION

Human brain performs certain functions which stands either unique or more improved in humans compared to other primate brains. This is incredibly achieved by making use of equal number of protein coding genes as in nematode, *C. elegans*, which surprisingly has only 302 neurons compared to the human brain, consisting 90 billon neurons and trillions of neural network. The human brain is, therefore, a prime example of an immense diversity and complexity of the human transcriptional landscape. This enhanced transcriptome complexity of human brain is achieved due to the intricate regulation and modulation of gene expression at different levels by diverse array of ncRNAs.[1-3]

ncRNAs play a predominantly significant role in the development and function of the human brain by altering the cellular expression of various genes both at the transcriptional and post transcriptional levels involving epigenetic modification, alternative RNA splicing, enhancer function, translation etc. The expression profiling studies have demonstrated the site - specific and stimulus- dependent regulation of the majority of ncRNAs in brain tissue. The ncRNAs are involved in plethora of neural tasks such as neuronal development and differentiation, synapse function, blood brain barrier formation and regulation, cellular homeostasis, stress response, neuronal plasticity, cognition and in controlling behavior.[4-15] The altered function of the ncRNAs, as demonstrated by the loss of function studies, leads to diseased and pathological outcomes in the brain such as Parkinson's disease, Alzheimer's disease, Huntington's disease, glioma, epilepsy, autism spectrum disorders, anxiety disorders, depression, schizophrenia etc.[16-23]

There exist strong evidences that different ncRNAs can make up a dependable tool for future use in brain disorders. The accessibility, high specifity and sensitivity

of ncRNAs along with the recent advancements in cutting edge sequence 'omics' technologies and single cell analysis techniques in understanding the molecular mechanisms of brain in physiological and pathological state, make these (ncRNAs) suitable candidates to be used both as ideal biomarkers and the therapeutic agents.[24,25]

TYPES OF ncRNAs: A DIVERSE CATEGORY

Noncoding RNA genes include introns, pseudogenes, repeat sequences, and cis and trans- regulatory elements that work as RNA without undergoing translation. The ncRNAs make up about 99% of the total RNA content in human cells, with validated RNAs increasing every year. These possess regulatory roles in various pathways of cellular biology in different organs by modulating chromosomal dynamics, chromatin architecture, cis and trans acting gene regulation, post transcriptional processing such as RNA splicing and translation, as well as in diseases initiation and progression.[26-31]

The ncRNAs classification is a continuous process because new ncRNAs continue to be discovered with the advancements in sequence technologies, functional studies and computational analysis. Nonetheless, classification of ncRNAs is done on their size, sequence and function (Figure 1). The class of ncRNAs which are constitutively expressed in all cell types is known as housekeeping ncRNAs. Examples include ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs) involved in protein synthesis; small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) which play pivotal roles in modification and processing of specific RNAs.[32,33]

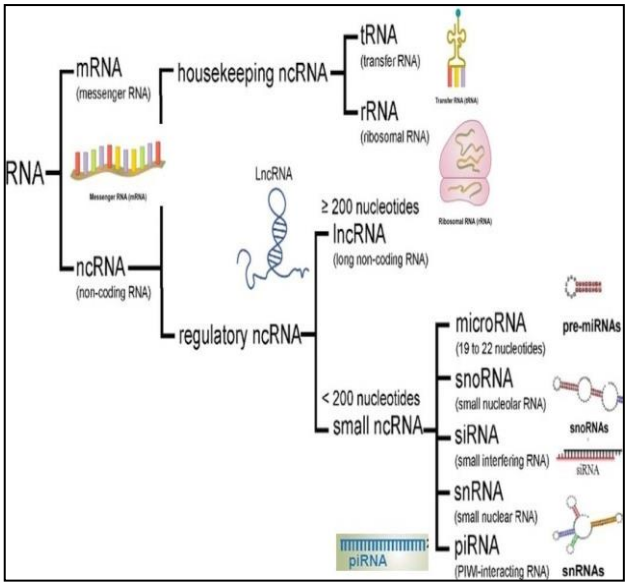

Figure 1: Types of RNA.

Recently, another class of ncRNAs which is regulatory in nature has gained attention of the researchers and is the focus of this article because of their significant role in brain development, memory storage and neurodegenerative disorders. This type of regulatory ncRNAs are categorized, based on their biological function and size, into two main groups: 1) Those which are linear in nature include short non coding RNAs (sncRNAs) and long non coding RNAs (lncRNAs); 2) Circular RNAs (cir RNAs), so called because of their circular structure formed due to covalently closed loop. sncRNAs are further subdivided into micro RNAs (miRNAs), small interfering RNAs (siRNAs), piwi interacting RNAs (piRNAs).[34,35]

Table 1: ncRNAs classification and their generalized functions in the cells.

ncRNA classes	Functions
Transfer RNAs (tRNAs)	Protein synthesis (Translate mRNA into protein); Adapter between the written genetic instructions and the protein products encoded in genes.[36]
Ribosomal RNAs (rRNAs)	Part of the ribosome; Assist in translating mRNA into protein.[37]
Micro RNAs (miRNAs)	RNA silencing by stimulating mRNA decay by using RNA induced silencing complex (RISC) in processing bodies (P bodies); Gene regulation at post-transcriptional level.[38]
Small or short interfering RNA (siRNA)	Post transcriptional gene silencing; Interfere gene expression by degrading mRNA (RNA silencing).[39]
Piwi-interacting RNAs (piRNAs)	Main role in gametogenesis and fertility; regulate gene expression by DNA methylation and transposons silencing.[40]
Small nucleolar RNAs (snoRNAs)	Act as Guide RNA in post transcriptional synthesis of other RNAs e.g. processing of rRNA.[41]
Small nuclear RNAs (snRNAs)	Processing or splicing of pre-mRNA; regulation of transcription factors and telomere length.[42]
Long ncRNAs (lncRNAs)	Epigenetic regulators primarily by methylation and acetylation; alternative splicing; mRNA stability.[43]
Circular RNAs (circRNAs)	Potential gene regulators and miRNA sponges and protein sponges, scaffolds and recruiters.[44]

BASIC CHARACTERISTICS OF ncRNAs, ORIGIN AND RNA INTERFERENCE

sncRNAs are generally less than 200 nucleotides in length and are the result of the cleavage of the longer primary transcripts including introns.[45] For example, micro RNAs (miRNAs) are 21 to 23 nt in length and participate in RNA silencing by base pairing to complementary sequence in the target mRNA which consequently is broken into two pieces or made unstable by shortening its poly A tail.[46,47]

miRNAs share many similarities with small interference RNAs (siRNAs) but differ from siRNAs in their origin from the folded regions within RNA transcripts making short hairpins (fold- back structure) whereas siRNAs are derived from the longer region of the double stranded RNA (dsRNA).[48] Both miRNAs and siRNAs are produced by the cleavage of precursor miRNAs (pre-miRNA) and the long double stranded RNA (dsRNA) respectively by the action of an endo- ribonuclease enzyme named Dicer. Dicer is a vital component of the multi protein complex, a ribonucleoprotein, named RNA induced silencing complex (RISC).[39,49] The newly formed miRNA and siRNA further act as an escort sequence (guide strand) for RISC to target its complementary mRNA transcript for gene silencing by cleavage and degradation using another vital protein called Argonaute in the RISC complex. This whole process is called as RNA interference (RNAi) (Figure 2).[50] miRNAs and siRNAs, thus, belong to a group of RNA interference molecules.

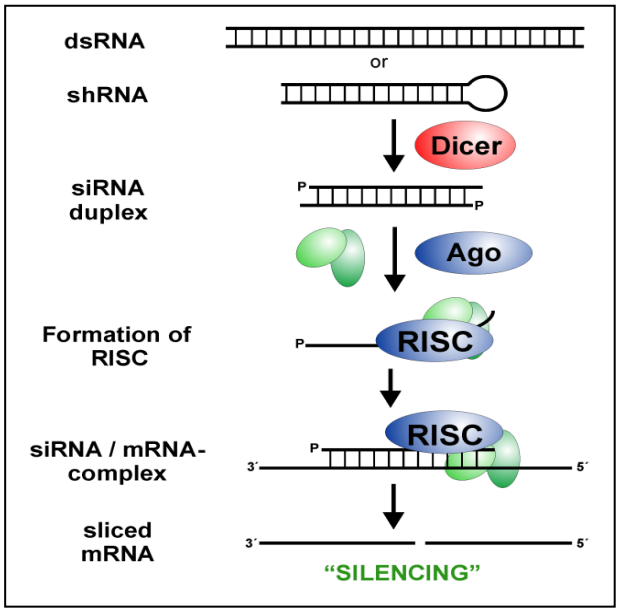

Figure 2: RNA interference mechanism: Dicer activates RNA interference process by facilitating the formation of RNA-induced silencing complex (RISC). RISC consists an endonuclease, named argonaute(Ago), which degrades mRNA molecule that match the sequence of siRNA guide strand.[153]

Piwi interacting RNAs (piRNAs) are a bit longer (26-31 nt) than miRNAs and differ from miRNAs in loss of sequence conservation, higher order complexity and their Dicer independent biogenesis.[51] piRNAs are formed from sense or antisense transposons thereby have sequence similar to their source. The evolutionary conserved PIWI family proteins cleave RNA into piRNA which forms RNA-protein complexes by associating with PIWIS (hence known as piRNA). piRNA directs the so formed ribo-protein complexes to attach the complementary transcripts targets for epigenetic and post- transcription silencing of transposons.[52]

Small nuclear RNAs (snRNAs) are generally 100-150 nt and coordinate transcripts splicing. snRNAs are mostly attached to ribonucleoproteins forming complexes known as small nuclear ribonucleprotien complexes (snRNP) such as U1, U2 and U3 spliceosomal RNA complexes based on the amount of uridine content.[53]

Small nucleolar RNAs (snoRNAs), are 50-300 nucleotides long. snoRNAs are produced by the exonuclolytic activities on longer precursor RNAs. These are involved in the site-specific chemical modifications like methylation (by C/D box snoRNAs) and pseudouridylation (by H/ACA box snoRNAs) of other RNAs particularly the pre-ribosomal RNAs (pre-rRNAs). These chemical modifications are necessary to form a functional tertiary structure of the rRNA. snoRNAs can also act as precursors for miRNAs.[54]

lncRNAs are transcripts longer than 200 nucleotides and are heterogeneous class of RNAs. Human genome encodes more than 35,000 lncRNAs, a number greater than the protein coding genes. Mostly, lncRNAs are produced like classic mRNAs via RNA polymerase II with all the characteristic signatures of mRNA production.[55] However, lncRNAs lack the protein coding ability (due to absence of open reading frame {ORF}), usually have low expression levels, inadequacy in sequence conservation and low conformity to RNA polymerase II relative to mRNA.[56,57]

CirRNAs can range from less than 100nt to more than 4kb and are dissimilar to all other non coding RNAs in lacking 5´ and 3´ ends because of their closed circular ring structure. The ring structure makes cirRNAs resistant to degradation by the exonucleases, leading to their higher stability compared to linear ncRNAs.[58] The closed cirRNAs have the ideal structure to function as topologically complex platform for the transportation of proteins or RNA.[59] miRNAs, lncRNAs and cirRNAs have mainly been observed as three crucial ncRNAs associated with human diseases though the role of other ncRNAs is also emerging and can't be underestimated. The ncRNAs may function autonomously or may interact with each other to coordinate the accurate control of gene expression, cellular signalling and genome stability for normal cellular functions (Figure 3). All these non coding

RNAs, thus, act as master regulators of the brain which is discussed in the following section.

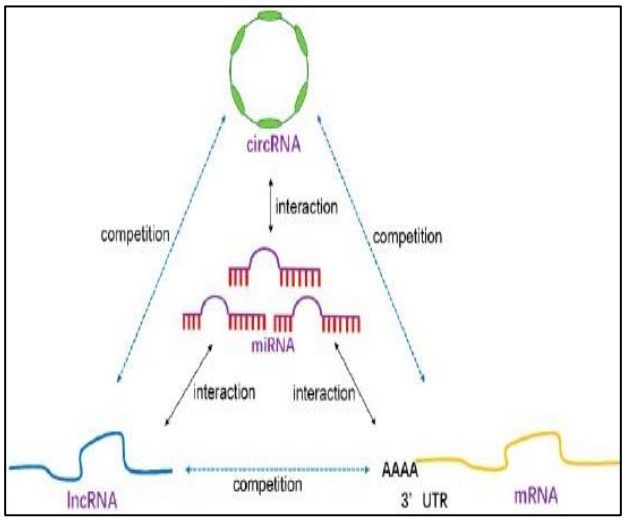

Figure 3: Interaction among ncRNAs (miRNA, lncRNA, and circRNA).[154]

NON-CODING RNAs AS REGULATORS IN THE BRAIN: NEURONAL DEVELOPMENT, DIFFERENTIATION, MAINTENANCE, MEMORY AND PLASTICITY

Human brain consists of large number of neuronal and glial cells. The brain to function in its complete form requires its extensive development and differentiation along with a proper cross talk between the extrinsic and intrinsic stimuli. The rapid evolution of brain development and differentiation in human, amongst all primates, is a consequence of the formation of distinct accelerated features called human accelerated regions (HARs) in the brain. HARs mostly fall in the non-protein coding areas of the genome.[60] These non-coding areas, which lack the protein coding capacity, play an outsize role in the brain, because of the fact that an immense transcriptional activity of the ncRNAs has been observed in neurons in a completely developed human brain.[61] ncRNAs have potential to modulate multiple genes expression triggering cascading effects, such as regulating cell cycle, protein synthesis etc., in brain development and differentiation. Most of the time ncRNAs account for genetic loci associated with the alterations in neuropsychiatric functions.[62]

The plethora of ncRNAs inclusive of miRNAs (miR-124, miR-125b, miR-21, miR-9), lncRNAs (Gomafu, Neat1) and circular RNAs (CDR1-AS) are highly expressed in a region or, cell-type-specific manner in the brain. The neurons and their synaptic junctions are rich in cirRNAs and miRNAs.[63-68]

sncRNAs have a distinct spatiotemporal differentiated expression in the human brain and are involved in embryonic neuronal differentiation. For example, the brain stem and cerebellum exhibit a very high expression of miR-124 which plays a significant role in their development and maintenance. miR-124 is abundantly expressed in initial stages of embryonic development and neuronal differentiation during adulthood, whereas miR-21 is more expressed in the microglia. miR-124 regulates neurogenesis, the neuronal processes on the developing neurons and synaptic plasticity.[64] miR-134 is transported to the axonal terminals and performs a vital role in synaptic plasticity and dendritic spine formation.[69] It is believed that phylogenetic expansion of miRNAs observed in humans may be an indispensable cause for physiological and neurological complexity that sets apart a human brain.[70]

The brain is the only somatic tissue besides the germline where piRNAs regulate the expression of L1 retrotransposons in the course of neuronal differentiation which causes neuronal heterogeneity as well as somatic mosaicism in brain.[71,72] The latter (mosaicism) plays an important role in behavior, cognition and neuro-developmental diseases like intellectual disability and autism spectrum disorder.[73]

The expression of several ncRNAs gets modulated by an increased neuronal activity or stress induced stimuli, pointing to their role in regulating neuronal plasticity. For example, an activity dependent turnover pattern in expression of miR-132 has been observed in neuronal cells than in non-neuronal cells.[74] Similarly, piRNAs, which function as epigenetic modifiers and have role in protein diversity, get modulated upon neural activation thereby, suggesting their link to memory storage.[75]

Circular RNAs also influence many brain functions such as neurogenesis, brain rhythmicity, neural cell fate determination etc. For example, cirRNA, cdr1-AS, acts as sponge and sequesters a micro RNA, mir-7, which is a regulator of neural development or neurogenesis.[76] Moreover, the rhythmic expression of cdr1-AS in the suprachiasmatic nucleus (a central circadian pacemaker in the brain) has been observed which influences the rhythmicity of the brain by interacting with proteins regulating clock genes.[77] Another circular RNA, cirFoxo3, associates itself with a RNA binding protein ID2 (Inhibitor of DNA binding/differentiation protein). This, in turn, inhibits ID2 regulated proteosomal degradation of the key transcription factors involved in neuronal differentiation of the progenitor cells to different types of neurons and glial cells.[78]

snRNAs like snRNA U1 regulates alternative splicing of exons during pre-mRNAs processing. The resultant splicing forms functionally specific neuronal isoforms which plays a vital role in synaptic connectivity by making appropriate circuit formation.[79] Many snRNAs like snRNA U1, U2 and U5 are involved in neuronal differentiation by being part of the molecular splicing complex, spliceosome, which in turn secure correct expression of the differentiation genes.[80] Similarly, small

nucleolar RNA(snoRNA), Snord115 targets the transcripts of serotonin receptor 5-HT2C to regulate its RNA editing and alternative splicing which if gets disrupted lead to a neuro developmental syndrome Prader-Willi syndrome(PWS), a disorder marked by behavioural and intellectual dysfunctions.[81] Another small nucleolar RNA termed Snord64 is sufficiently expressed in the cerebellum and regulates the synthesis of small nucleolar ribonucleoproteins (snoRNPs) involved in ribosome assembly and rRNA processing. Interestingly, Snord64 knockout mice exhibits impaired synaptic plasticity in cerebellum and motor co-ordination deficits.[81]Similarly, neuronal knockdown of Snord50A results in decreased dendritic spine density leading to impaired synaptic transmission and neuronal circuitry.[82]

The lncRNA like BDNF-AS regulates neuronal development and plasticity and are found in the axonal distal ends. BDNF-AS is a natural antisense transcript to brain derived neurotrophic factor (BDNF) mRNA and regulates its expression and axonal development (Figure 4).[83] lncRNA Gm38257, termed ADEPTR (for activity-dependent transported lncRNA), binds and forms complexes with proteins responsible for synaptic organization which causes alternation in dendritic structure, when moved by the cell's cytoskeleton to tips of hippocampal neurons. The experimental knockdown of this lncRNA in mice led to a reduced neuronal plasticity in response to activity.[84]A specific lncRNA, GM12371, regulates several genes linked to the shape and signaling capacity of the developing neurons as part of the CNS development and functioning. The learning related signal in mouse hippocampal cells up-regulates the expression of GM12371 whereas its reduction results in inactive neurons.[85]

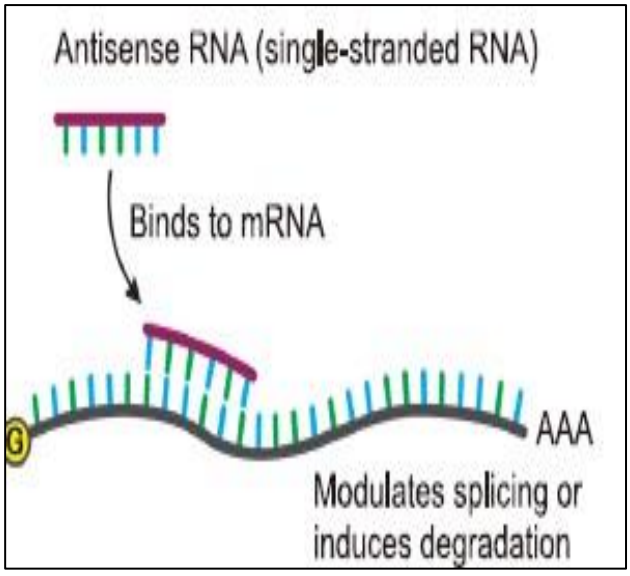

Figure 4: Mechanism of antisense RNA based mRNA silencing: Single stranded antisense RNA binds to either pre–mRNA or mature mRNA resulting in altered splicing or degradation respectively, rendering them nonfunctional and hence called 'silenced'.[155]

ncRNAs AND NEUROLOGICAL DISEASES

A few studies discussed in the previous section have demonstrated that ncRNAs modulate high level of neuronal gene expression through a diverse array of mechanisms involving chromatin modification, transcription, splicing and translation which consequently regulate vital brain functions such as its development, differentiation, cellular homeostasis, behavior, cognition, synapse formation as well as plasticity. It is therefore not unusual to find that the dysfunction or mutations in the regulatory mechanisms of ncRNAs in the brain are linked to a spectrum of neurodegenerative and brain disorders.[86-89] Therefore, the present section is aimed to discuss briefly the link between ncRNAs and a few of these diseases.

Parkinson's disease

The extensive research so far engaged protein coding genes and their role in neurodegenerative Parkinson's disease (PD) which is marked by the gradual loss of dopaminergic neurons in substantia nigra region in the brain. Recent studies, however, exhibit the role of ncRNAs in PD as well. Micro RNA, miR-133b which modulates the expression of the genes involved in dopamine biosynthesis like tyrosine hydroxylase (TH) and vesicular monoamine transporter2 (VMAT2) is dysregulated in the dopaminergic neurons in PD patients, thereby contributing to neuronal dysfunction and degeneration in PD.[90] SNCA-AS1, a lncRNA transcribed from the antisense strand of the alpha- synuclein (SNCA) gene regulates the expression of SNCA gene and is found to be increased in familial forms of PD. Elevated levels of SNCA-AS1 enhance alpha- synuclein aggregation and neurotoxicity which contribute to pathogenesis of PD.[91] Familial and sporadic PD is also associated with the mutations in the leucine rich repeat kinase 2 (LRRK2) gene. The expression of LRRK2 is regulated by a ncRNA named LRRK2 antisense transcript, and is involved in PD pathogenesis.[92] Similarly, the lncRNA HOTAIR (Hox transcript antisense RNA) also interacts with LRRK2 and alters its expression and protein level.[92] Metastasis associated lung adenocarcinoma transcript1 (MALAT1), a lncRNA is upregulated in PD brains and causes mitochondrial dysfunction and oxidative stress which gets attenuated in MALAT1 knockdown experimental studies.[93]

Alzheimer's disease

The recent studies have brought forth the role of ncRNAs in Alzheimer's disease (AD) besides the already existing various molecular and cellular mechanisms central to AD. The dysregulation of miRNAs, involved in regulating gene expression of target mRNAs, lead to aggregation of amyloid β protein (Aβ) and tau protein hyper-phosphorylation which consequently play a vital role in pathogenesis of AD. For example, miR-29a expression is decreased in AD brains. This miRNA

targets a beta secretase enzyme, BACE1, responsible for Aβ production and the decreased levels of miR-29a promotes Aβ accumulation.[94] miR-132 known to modulate synaptic plasticity and memory formation is also down regulated in AD contributing to cognitive impairment in AD.[95] lncRNA BACE1-AS, is a natural antisense transcript of BACE1(beta-site amyloid precursor protein cleaving enzyme) and is a negative regulator of BACE1 expression. Therefore, the decreased level of BACE1 anti sense transcript in AD results in increased BACE1 expression resulting in Aβ accumulation.[96]

lncRNA MALAT1 discussed above in PD is also involved in pathogenesis of AD. The dysregulation of MALAT1 is linked to higher 'tau' phosphorylation and neuronal apoptosis, both of which are key components of AD pathogenesis.[97] A circRNA, circHIPK3 is a sponge for miR-124 which in turn targets BACE1. circHIPK3 by sequestering miR-124 indirectly upregulates BACE1 expression and Aβ production in AD brains.[98]

miRNAs have also been shown to differentiate between diseases subtypes in PD and AD and can be used as markers for classification of the disease. For example, around 30 differentially regulated miRNAs have been observed in the brain and blood of AD patients who were appropriated to different Braak stages, a method to classify AD pathology. Ten miRNAs named hsa-miR-107,26B,30e,34a,485,200c,210,146a,34c and mir-125b are exclusively associated with Braak stage III.[99] Similarly, miR-331-5p is differentially expressed in plasma of early onset Parkinson's disease (EOPD) which was not found in late onset Parkinson's disease (LOPD) patients.[100]

Autism spectrum disorder

Recent studies have demonstrated the association of ncRNAs in the pathogenesis of the autism spectrum disorder (ASD). For example, the decreased levels of miR-132, involved in neuronal development and synaptic functions, has been observed in the postmortem samples of ASD individuals.[101] The overexpression of lncRNA H19 in ASD brains is thought to modify dendritic spine morphology and altered synaptic function, contributing to synaptic abnormalities observed in ASD.[102] CirRNA Cdr1-AS (also known as ciRS-7) sequesters miR-7 and has been found to be upregulated in ASD. miR-7 plays a vital role in neuro developmental processes. Cdr1-AS by sequestering miR-7 therefore disrupts the regulation of genes targeted by miR-7, resulting in abnormal neuronal development and synaptic function associated with ASD.[103]

Huntington disease

Huntington's disease (HD), an autosomal dominantly inherited devastating neurodegenerative disorder, is mainly the result of mutation in the huntingtin (HTT) gene. The recent studies, however, have highlighted the intricate role of ncRNAs in its pathogenesis. miR-124 expression levels are significantly down regulated in the brains of HD patients and animal models which consequently up-regulates the target genes involved in neuro-inflammation.[104] The down regulation of microRNAs like hsa-miR-98 (hsa*:* Homo Sapiens) and over expression of hsa-miR-323b-3p has also been observed in HD subjects compared with healthy inviduals.[105] Huntigton antisense (HTTAS) is a natural antisense transcript of the HTT gene and its overexpression in a cultured cell system reduces the transcriptional level of HTT gene.[106] The levels of HTTAS are found to be reduced in the frontal cortex of HD patients thereby implicating the role of HTTAS in HD pathology.[107]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) also called as Lou Gehrig disease, is a neurodegenerative disorder affecting motor neurons of the brain and the spinal cord. The ncRNAs have recently got the attention of the researchers in the pathogenesis of ALS. miR-155 expression is up-regulated in astrocytes of ALS patients and mouse models.[108] It results in the impaired glutamate uptake due to the reduced expression of astrocyte glutamate transporter GLT-1 leading to excitotoxicity. Excessive levels of glutamate damage the motor neurons and increase ALS progression.[109] The up-regulated miR-155 is known to down-regulate transcription factor MEF2D (myocyte enhancer factor).[110] MEF2D is one of the key factors in neuronal survival and function. The reduced level of MEF2D therefore affects motor neuron survival resulting to their degeneration. Nuclear paraspeckle assembly transcript 1 (NEAT1), a lncRNA, known to form nuclear paraspeckles and modulate RNA processing is up regulated in motor neurons in ALS. The upregulation of NEAT1 sequesters RNA binding protein including SFPQ in paraspeckles. SFPQ is an emerging RNA binding protein having vital functions in neuronal development and homeostasis which get impaired with increased levels of NEAT 1 in ALS.[111]

Schizophrenia

Schizophrenia (SCZ) is a complex neuropsychiatric disorder with a wide array of neuro-cognitive impairments. The different types of ncRNAs have been implicated in its pathogenesis. For example, miR-137 is downregulated in brains of SCZ patients. miR-137 is a brain-enriched miRNA in humans with a high level of expression in the cortical brain regions, and hippocampus and low expression in cerebellum and brain stem. miR-137 regulates various genes, such as CACNAC1 and TCF4, connected with synaptic plasticity and neurodevelopment. The altered levels of miR-137 derange these pathways resulting in disrupted neural circuitry and cognitive impairment associated with schizophrenia.[112,113] A long intergenic non-coding RNA

(lincRNA) named H19 is abnormally expressed in schizophrenia patients. It alters the DNA methylation patterns of genes involved in synaptic functions and neural differentiation leading to pathogenesis of schizophrenia.[114] A particular lncRNA of interest is Gomfau, also known as MIAT or RNCR2, is downregulated in SCZ upon neuronal activation. Gomfau modulates several molecular pathways in neuronal development and interruption to these path ways may contribute to the pathogenesis of SCZ.[115, 116]

Major depressive disorder

Major depressive disorder (MDD) is a persistently depressed mood disorder which limits psychosocial functioning and impairs quality of life. The various studies have demonstrated that micro RNAs such as miR-16,124,128,139 and 144 play an important role in patho physiological mechanisms of major depressive disorder.[117] miR-16 is a widely studied miRNA in MDD which regulates the genes associated with serotonin signaling such as the serotonin transporter (SERT). miR-16 levels are down-regulated in the rat model of depression which causes increased expression of SERT leading to decreased serotonin availability.[118,119] hsa _cirRNA_103636 level is down regulated in mononuclear cells of MDD patients versus healthy control which gets altered after two months of antidepressant regimens, suggesting its use as a potential biomarker for MDD.[120] The vast number of similar studies exist in the literature which demonstrate that the dysregulation of different types of ncRNAs play a significant role in the pathogenesis of various neurological diseases resulting in impaired brain function and neurological symptoms. ncRNAs have, infact, provided us a valuable deep understanding of the molecular mechanisms and their roles in these complex disorders, consequently leading to the development of their use as potential biomarkers and therapeutics in neurological and brain disorders which are discussed in the following sections.

ncRNAs AS BIOMARKERS IN NEUROLOGICAL CONDITIONS

The neurological and brain disorders are diagnosed and monitored primarily on the basis of clinical symptoms (which can be subjective and variable), neuropsychological assessments, imaging and other laboratory tests. There is a demanding requirement of dependable and authentic biomarkers to make an early diagnosis, track progression of the diseases and for the advancements in target therapies. The recent advancements in high throughput sequencing techniques, bioinformatics, machine learning and the longitudinal studies have aided the identification of novel ncRNAs as biomarkers. The studies have shown, and are still expanding, that ncRNAs can be promising biomarkers in neurological and brain disorders because of their vital role in plethora of cellular processes along with their capability to reflect occurrence and progression of the disease.

The lab studies have shown that it can either be a specific ncRNA or a group of ncRNAs to be essential, for identification of a specific neurological disorder, for enhanced diagnostic sensitivity and/or specificity. For example, the level of micro RNA, miR-34b which regulates the genes linked to pathogenesis of PD, such as alpha synuclein (SNCA) and Parkinson's disease protein -7 also known as DJ1, is persistently decreased in the blood, CSF and brain of PD patients making it a promising diagnostic biomarker.[121-123] The blood level of lncRNA, HOTAIR, which is over expressed in PD and is involved in dopaminergic neuron degeneration can also be used as blood based biomarker in PD.[124,125] The low expression of miR-132, in the CSF of AD patients, which mediates Aβ metabolism and synaptic plasticity in AD can be a promising diagnostic biomarker for AD.[126]

BACE1-AS, the lncRNA, a negative regulator of BACE1 which is responsible for Aβ production is dysregulated in AD and is a suggestive biomarker for AD.[127] CdR1- AS acts as a miR-7 sponge and regulates processing of amyloid precursor protein and Aβ production. The dysregulation of CdR1-AS is observed in AD and is, therefore, currently explored as a diagnostic marker in AD.[128] The miRNA miR-320a is down regulated in the peripheral blood and serum of ASD patients which might be a good candidate for noninvasive biomarker for ASD.[129] miR-10b-5p which has a pathological role in expanded polyglutamine repeat of HD and in BDNF regulation has been found to be elevated in plasma of HD individuals thereby suggesting its use as a clinical biomarker for HD.[130]

The increased expression of miR206, which plays an important role in muscle development and regeneration, has been observed in CSF of ALS patients and shows promise as a potential diagnostic biomarker for ALS.[131] miR-22-3p, miR-92a-3p, and miR-137 are aberrantly expressed in the peripheral blood mononuclear cells of schizophrenia patients and are upcoming biomarkers for SCZ.[132] lncRNAs NEAT1 and NEAT2 are down regulated in peripheral blood of SCZ patients which gets up-regulated after treatment which is suggestive of their potential as good diagnostic biomarkers.[133] The depressed patients have the reduced level of miR-200a, miR-200b , miR 218 and miR200c in their blood compared to healthy controls and also increased levels of miR-221 which might serve as potential diagnostic biomarkers.[134] The ncRNAs though are emerging as potential diagnostic biomarkers for neurological diseases but these are still far from clinical translation and are in early stages of research and development. The identification of clinically approved ncRNAs as biomarkers, requires substantial evidences from well-designed clinical trials to validate the diagnostic accuracy and to ensure their sensitivity and specificity for diagnosing neurological disorders.

THERAPEUTICS IMPLICATIONS OF ncRNAs IN NEUROLOGICAL DISORDERS

The treatment of neurological disorders remains challenging with focus mainly on managing symptoms and an attempt to slow down the progression rather than a cure. The ncRNAs along with the approaches to engineer the ncRNAs for therapeutic use are rapidly emerging to treat neurological diseases due to their (ncRNAs) regulatory role in various cellular processes and pathogenesis of these diseases. A mimic or an antagonist of a ncRNA could be analyzed as therapeutic agent depending upon the existing research data available on the role a ncRNA in the pathogenesis of a particular neurological disease. For example, miR-124 is down regulated in PD and studies using miR-124 mimics in animal models of PD proved neuro protective by stimulating neuronal survival and reducing inflammation.[135] lncRNA HOTAIR, associated with increased oxidative stress and neurotoxicity in PD, when silenced using antisense oligonuclotide (ASO) to HOTAIR results in improved motor functions in PD models.[136,137]

An increased 'tau' expression has been implicated in the pathogenesis of Alzheimer disease (AD).A clinical trial to test an antisense oligo nucleotide (ASO) targeting tau RNA in patients with mild AD, is under study by Biogen, INOIS Pharmaceuticals (NCT03186989), based on the results that injection of this particular ASO into the CSF of nonhuman primates reduced the expression of target tau RNA in brain regions including hippocampus.[138] Similarly, non- coding antisense transcript for β secretase-1 enzyme (BACE1-AS) regulates BACE 1 mRNA expression which causes amyloid β protein accumulation in AD. The targeting of BACE1-AS with an antisense (ASO) led to reduced BACE1 levels and Aβ accumulation in AD mouse model, indicating its therapeutic potentials.[139] Generally the ASOs that targets natural antisense transcripts in the neuronal cells results in inducing the brain derived neurotrphic factor (BDNF) *in vivo* leading to improved neurological outcomes.[140]

NEAT1 increases Aβ induced neuronal damage by targeting miR-107 in Alzheimer disease. Silencing of lncRNA NEAT1 attenuates Aβ-induced inhibition of viability and promotion of apoptosis and tau protein levels in established AD neuro blastoma cell lines, suggesting it as a therapeutic target.[141] RNA interference based strategies using small interfering RNA to lncRNA, Gomafu, in preclinical models of autism spectrum disorder (ASD) led to behavior improvements.[142] RNAi strategies to reduce mutant human htt gene expression, improved the motor and neuro pathological abnormalities in Huntington's disease mouse model and cell culture.[143] The use of antisense oligonucleotides ISIS 333611 delivered intrathecally against SOD1 familial amyotrophic lateral sclerosis, in a phase1 randomised first in man study, decreased the SOD1 mRNA and protein concentration in spinal cord tissue and prolonged the survival.[144] Recent study has demonstrated that piRNA can facilitate the entry of anti-glioma drugs in the blood -brain barrier , opening a novel strategy for the entry of new drugs to glioma cells.[145] ASO drug HD, RG6042, previously called as IONIS-HTTRx, has been sown to inhibit mutant HTT protein production in CSF and is in the phase III clinical trials. RG6042 (known by the brand name Tominersen® by Roche) modulates RNase H1 induced degradation of mutant HTT mRNA.[146]

There exist multiple studies on the therapeutic applications of ncRNAs in the neurological disorders but mostly are either the lab researches or a few in the initial stages of preclinical trials.[147-150] The therapeutic uses of ncRNAs in these disorders' present various challenges despite the significant advancements in understanding their roles in neurodevelopment, synaptic plasticity and neuronal functions. One of the primary challenges is the efficient delivery of ncRNAs through the blood brain barrier which limits the passage of large molecules. The development of efficient delivery systems, such as viral and non-viral vectors and nano-based inorganic particles etc., to transport safely and specifically the ncRNAs is critical for a successful outcome. Specificity is a big concern for safe and effective ncRNA based therapeutics as ncRNAs target multiple genes which may result in off target effects by interfering in vital endogenous cellular processes. The off targets effects could derange the normal cellular processes and can probably exacerbate the disease. The selection of accurate ncRNA, amongst the thousands of identified ncRNAs, for therapeutic development is also an immense challenge. This can be achieved only when functional mechanism of each ncRNA along with its involvement in the pathophysiology of a particular neurological and brain disorder are fully comprehended.[148,151,152]

CONCLUSION

ncRNAs have come up as central regulators of gene expression and cellular processes within the brain with multifaceted functions to play varying from neuronal development and synaptic plasticity to neurodegeneration. The study of ncRNAs in neurological and brain disorders is a rapidly developing area having immense promises to further our knowledge of brain functions and upgrade the diagnosis and treatment. There can be a transformative shift in future in our understanding and outlook to manage these disorders, as the research in the field of ncRNAs accelerates. There is, thus, a need for a collaborative work between interdisciplinary researchers, clinicians and biotech pharmaceutical industry collaborators to exploit the full potential of ncRNAs for diagnosis and treatment of neurological diseases by developing efficient delivery systems, improving safety and specificity and minimizing off targets effects. Once these issues get addressed, the use of ncRNAs as novel biomarkers and therapeutic targets in future will surely empower timely interventions and personalized management of neurological and brain

disorders, thereby improving the lives of millions of patients affected worldwide.

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