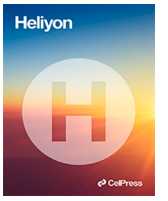
Heliyon 10 (2024) e39036

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Decoding the molecular script of 2′-O-ribomethylation: Implications across CNS disorders

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ARTICLE INFO

Keywords:
Ribosome
2′-O-Methylation
Modification
Translation
Protein synthesis
rRNA
fibrillarin
snoRNA
Neuropsychiatric disorders

ABSTRACT

Emerging evidence underscores the critical role of impaired mRNA translation in various neurobiological conditions. Ribosomal RNA (rRNA), essential for protein synthesis, undergoes crucial post-transcriptional modifications such as 2′-O-ribose methylation, pseudouridylation, and base modifications. These modifications, particularly 2′-O-ribose methylation is vital for stabilizing rRNA structures and optimizing translation efficiency by regulating RNA integrity and its interactions with proteins. Concentrated in key regions like decoding sites and the peptidyl transferase center, dysregulation of these modifications can disrupt ribosomal function, contributing to the pathogenesis of diverse neurological conditions, including mental health disorders, developmental abnormalities, and neurodegenerative diseases. Mechanistically, 2′-O-ribose methylation involves interactions between small nucleolar RNAs (snoRNAs), snoRNPs, and fibrillarin, forming a complex regulatory network crucial for maintaining ribosomal integrity and function. Recent research highlights the association of defective ribosome biogenesis with a spectrum of CNS disorders, emphasizing the importance of understanding rRNA mechanisms in disease pathology. This review focuses on the pivotal role of 2′-O-ribose methylation in shaping ribosomal function and its potential implications for unraveling the pathophysiology of CNS disorders. Insights gained from studying these RNA modifications could pave the way for new therapeutic strategies targeting ribosomal dysfunction and associated neuropathological conditions, advancing precision medicine and therapeutic interventions.

1. Introduction

Ribosomes are fundamental molecular machines present in all living cells, playing a pivotal role in cellular protein biosynthesis [1]. Comprising ribosomal RNA (rRNA) and ribosomal proteins, these macromolecular complexes are essential for translating the genetic code from messenger RNA (mRNA) into functional proteins. The structural integrity and function of ribosomes are heavily dependent on the rRNA, which not only acts as a scaffold for ribosomal proteins but also plays a crucial role in catalyzing key steps in the translation process. In mammals, rRNAs orchestrate various cellular activities, extending their functional repertoire beyond protein synthesis to include roles in cellular homeostasis, metabolism, and stress response mechanisms.

In eukaryotic cells, the ribosome has two subunits: the large (60S) and the small (40S) subunits. The 60S subunit, containing three rRNAs (5S, 5.8S, and 28S) and 47 ribosomal proteins, houses the peptidyl transferase center (PTC) [2], where peptide bonds are

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https://doi.org/10.1016/j.heliyon.2024.e39036
Received 26 July 2024; Received in revised form 17 September 2024; Accepted 4 October 2024
Available online 5 October 2024

formed between amino acids, elongating the nascent polypeptide chain. The small 40S subunit contains one rRNA (18S) and 33 ribosomal proteins and is responsible for decoding mRNA and ensuring the correct positioning of transfer RNA (tRNA) during translation [2]. These subunits work together in a highly coordinated manner to ensure the accurate and efficient synthesis of proteins. The PTC, decoding site, and translation factor binding sites within these subunits are evolutionarily conserved, emphasizing their critical role in maintaining translational fidelity and efficiency across species [1–5].

The brain, as one of the most complex and metabolically active organs, relies heavily on the precise regulation of protein synthesis. A finely tuned balance of protein homeostasis is required to generate, organize, and sustain the intricate network of neural connections, a process central to brain development, plasticity, and higher cognitive functions. Any disruption in this delicate balance can

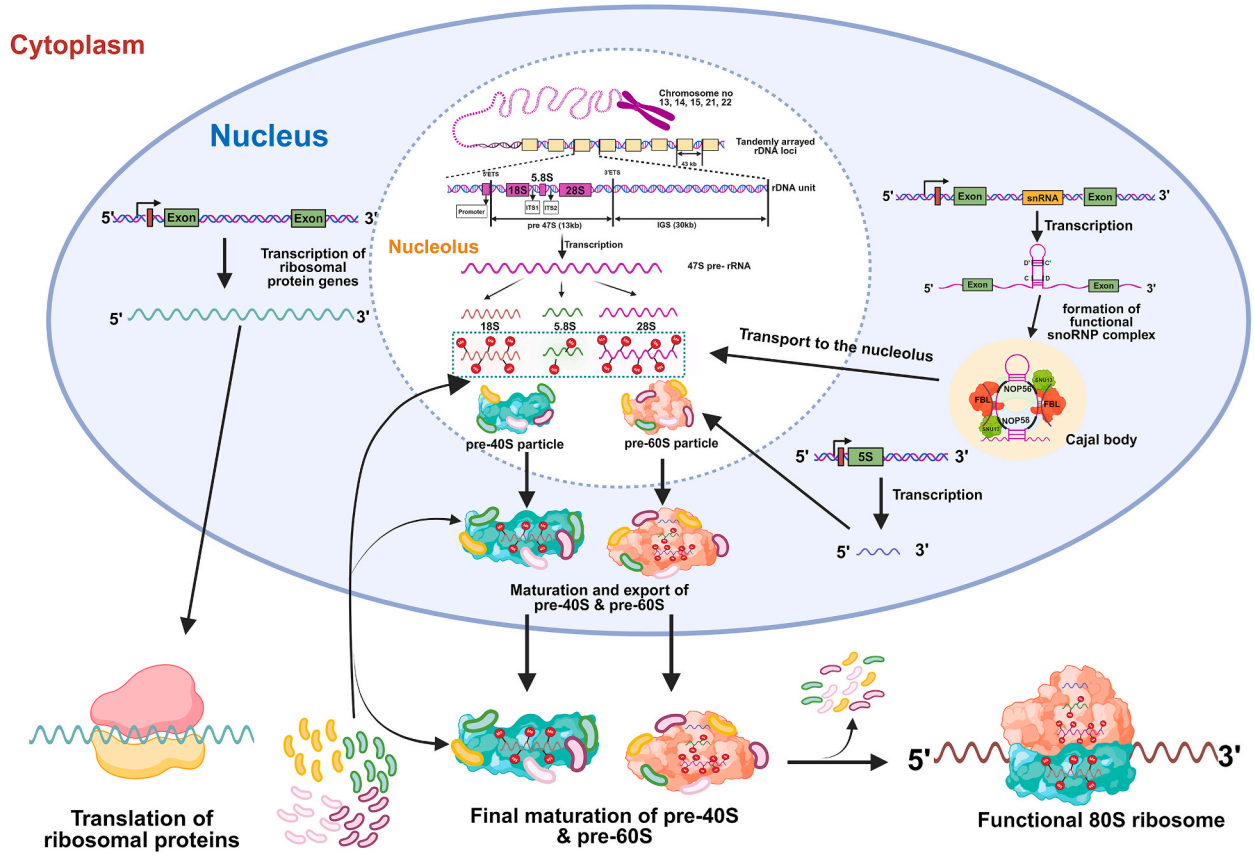


Fig. 1. The Path to Mammalian Ribosome Biogenesis. This diagram presents a comprehensive overview of ribosome biogenesis in human cells, emphasizing the intricate and coordinated interplay between the nucleolus and the cytoplasm throughout the process. Ribosome biogenesis consists of four major stages: transcription and initial processing of ribosomal RNA (rRNA), assembly of ribosomal proteins with rRNA, export of pre-ribosomal subunits to the cytoplasm, and final maturation into the 40S and 60S subunits. The process begins in the nucleolus, where RNA polymerase I transcribes ribosomal RNA genes to generate a polycistronic 47S precursor rRNA (pre-rRNA). At this stage, this pre-rRNA can undergo co-transcriptional modifications, such as methylation and pseudouridylation, facilitated by small nucleolar ribonucleoproteins (snoRNPs) and various processing factors. Endo- and exonucleases then process the pre-rRNA, dividing it into 18S, 5.8S, and 28S components. In the next stage, ribosomal proteins are synthesized in the cytoplasm and imported into the nucleolus, where they assemble with the processed rRNA. This assembly is assisted by small nucleolar RNAs (snoRNAs) and a range of protein assembly factors, leading to the formation of the 90S pre-ribosome. This large complex is subsequently divided into the pre-40S subunit and the pre-60S subunit. Once assembled, the pre-ribosomal subunits are translocated from the nucleus to the cytoplasm through nuclear pore complexes, guided by specific export receptors and adaptor proteins. In the cytoplasm, these pre-ribosomal subunits undergo final cleavage, modifications, and quality control processes to mature fully. The pre-40S subunit matures into the functional 40S small subunit, while the pre-60S subunit matures into the functional 60S large subunit. These two subunits then combine to form the mature 80S ribosome complex, fully prepared for its critical role in protein synthesis. Ribosome biogenesis requires precise and coordinated regulation of the transcription of rRNA, mRNA, and tRNA by three distinct RNA polymerases. RNA polymerase I transcribes the polycistronic 47S pre-rRNA, which is processed into the 18S, 5.8S, and 28S rRNAs. RNA polymerase III transcribes the 5S rRNA and tRNAs, while RNA polymerase II handles the transcription of ribosomal protein genes. These ribosomal proteins, categorized into small (RPS) and large (RPL) subunits, are translated into the cytoplasm and imported into the nucleolus, where they are incorporated into their respective subunits. The diagram captures the elaborate orchestration of ribosome biogenesis, emphasizing its complexity and critical role in protein synthesis and cellular growth. It underscores the highly regulated nature of this process, ensuring that each stage progresses in a controlled manner to produce functional ribosomes essential for the cell's translational machinery.

result in neurological dysfunction, contributing to a wide range of CNS disorders, including developmental, psychiatric, and neurodegenerative diseases. The mammalian nervous system is particularly adept at plasticity—the ability to form and reorganize synaptic connections in response to learning and memory demands. Given the immense energy demands of maintaining this plasticity, the brain depends on a tightly regulated process of ribosome biogenesis to meet the constantly shifting requirements for protein synthesis.

Ribosome biogenesis is an intricate, multi-step process that involves the coordinated activity of three RNA polymerases (I, II, and III), ribosomal proteins, and several non-ribosomal factors, including small nucleolar ribonucleoproteins (snoRNPs) [6]. This assembly process is highly organized and energy-intensive [6], involving transcription, processing, modification, and folding of rRNA before the ribosomal subunits can be assembled. One critical step in ribosomal maturation is the post-transcriptional modification of rRNA, which fine-tunes the structure and function of the ribosome. Among the many rRNA modifications, 2′-O-ribose methylation, which occurs primarily at specific positions within the rRNA, is particularly important for maintaining ribosomal integrity and optimizing translational output.

2′-O-methylation of rRNA, catalyzed by a complex of snoRNAs and the methyltransferase fibrillarin, plays a critical role in stabilizing rRNA structure and facilitating proper interactions between rRNA and ribosomal proteins. This modification is concentrated in key functional regions of the ribosome, such as the PTC and the decoding site, where it enhances the fidelity and efficiency of protein synthesis [7,8]. Dysregulation of 2′-O-methylation can lead to structural and functional defects in ribosomes, which in turn can impair translation and cellular homeostasis [9]. Recent research has revealed that such defects are associated with a range of brain disorders, including intellectual disabilities, neurodevelopmental disorders, and neurodegenerative diseases [10].

In addition to its role in stabilizing rRNA, emerging studies suggest that 2′-O-methylation exhibits a degree of plasticity, allowing the ribosome to adopt different functional conformations in response to cellular signals or environmental changes [11]. This dynamic regulation of ribosomal activity may be particularly relevant to the mammalian nervous system, where rapid adjustments in protein synthesis are essential for neuronal plasticity and cognitive functions. Aberrations in 2′-O-methylation and other epitranscriptomic modifications of rRNA have been linked to defects in synaptic function, learning, and memory, highlighting the importance of this modification in brain health and disease [12–14].

This review aims to provide a comprehensive overview of the role of 2′-O-methylation in ribosome biogenesis, with a specific focus on its potential involvement in the pathophysiology of neurological disorders. We will explore how this epitranscriptomic modification regulates ribosome function and fidelity, and discuss its broader implications for CNS disorders, including neurodevelopmental and neurodegenerative diseases. By understanding the molecular mechanisms underlying rRNA modifications such as 2′-O-methylation, we may uncover new therapeutic targets for treating brain diseases associated with ribosomal dysfunction.

1.1. Ribosome biogenesis

Eukaryotic cells are quite complex as compared to prokaryotes and archaea. Their demand for protein is much higher. The only way to fulfill the need for more protein is to increase the number of ribosomes. As is well known, ribosomes are complex macromolecules, and their biogenesis is multifaceted and energy-demanding [6]. A schematic representation of ribosome biogenesis is depicted in Fig. 1. Eukaryotic cells are highly compartmentalized, and ribosome biogenesis does not occur in one place. It starts in the nucleolus, then the nucleus, and is finalized in the cytosol [2]. Ribosomal RNA is transcribed from ribosomal DNA (rDNA) and then bound to ribosomal proteins to form small and large ribosome subunits. Ribosome biogenesis begins with the transcription of polycistronic pre-RNA by RNA polymerase-I [15]. Mammalian RNA polymerase-I is made up of 13 subunits (14 subunits in Saccharomycotina species), ten core subunits (Replication Protein A: RPA1, RPA2, RPAC1, RPAC2, RPABC1, RPABC2, RPABC3, RPABC4, RPABC5, RPA12), two constitutive subunits (RNA polymerase I associated factor: PAF53, PAF49) and one stack subunit (RPA43) [16]. RNA polymerase-I is located in the nucleolus, a distinguished nuclear compartment, and produces a single transcript of 47S pre-ribosomal RNA (pre-rRNA) [17]. Later, this 47S pre-ribosomal RNA is spliced, generating 28S, 18S, and 5.8S rRNA. Meanwhile, the 5S rRNA is synthesized by RNA polymerase-III [18].

In human cells, more than three hundred rRNA gene copies (approximately 150 copies in yeast) are present. All are not located on the same chromosome [19]. The 47S rRNA genes are located in the short arm of acrocentric chromosomes 13, 14, 15, 21 & 22 [20], and the 5S rRNA genes are located on chromosome 1 [21]. The length of the mammalian rRNA gene is 45 kb [22]. On the contrary, in yeast, it is only 9.1 kb [23]. Each rRNA gene has an internal transcribed spacer (ITS) and intergenic spacers (IGS), pivotal in rRNA maintenance. Additionally, several R repeats are present at the end of the rRNA genes, uniquely serving to terminate the rRNA transcription [20]. The R repeats are specific sequences (~680 bp, three copies) located in the termination region of the rRNA gene. These repeats contain Sal-boxes, which are crucial for the rRNA transcription termination. This Sal box is associated with transcription factor TTFI to inhibit the replication fork to avoid the collision of RNA and DNA polymerase [20]. During transcription, recruiting RNA polymerase I to the promoter region of ribosomal RNA (rRNA) genes is a complex task. It is accomplished with the assistance of a crucial transcription factor, RRN3, which acts as a guide, directing the polymerase to the precise site for efficient initiation [24].

Mammalian rRNA promoters are structured with two key regulatory elements: the upstream control element (UCE) and the core element (CE) [25]. The UCE, bound by the upstream binding factor (UBF), triggers transcription by binding to specific DNA sequences. UBF, homologous to yeast upstream activation factor (UAF), plays a vital role in bending DNA, introducing a loop that facilitates the assembly of other transcription factors at the promoter region. This looping structure allows transcription factors to interact efficiently, even if they are initially bound to sites far from the gene they regulate [26]. The CE bound by selectivity factor 1 (SL1) forms a complex with the TATA-binding protein (TBP) to initiate precise transcription [24,27,28]. The CE is surrounded by the ribosomal initiator element (rInr). This sequence aids in recruiting TBP-containing transcription factors, thereby enhancing the transcriptional machinery's binding affinity and ensuring accurate and robust initiation of rRNA gene transcription. However, rRNA genes encode ribosomal

RNA and rRNA gene promoter methylation, determines rRNA transcription, a study examined if epigenetic differences in critical loci associated with rRNA genes could be involved in the pathophysiology of suicide. It was found that rRNA was significantly hypermethylated throughout the promoter and 5′ regulatory region in the hippocampus of suicide subjects, which was associated with reduced rRNA expression, suggesting that epigenetic modulation of rRNA could be involved in the pathophysiology of suicide. Additionally, aberrant rRNA processing, ribosome biogenesis, and translation control mechanisms have also been observed in postmortem brain and cellular models of psychiatric disorders, suggesting a link between disrupted ribosomal function and neuronal dysfunction [29]. As shown in Fig. 4, the biosynthesis of ribosomes under normal conditions involves several key steps, including rRNA transcription, modification, and assembly (Fig. 4A). However, altered 2′-O-methylation of rRNA leads to disrupted ribosome biogenesis

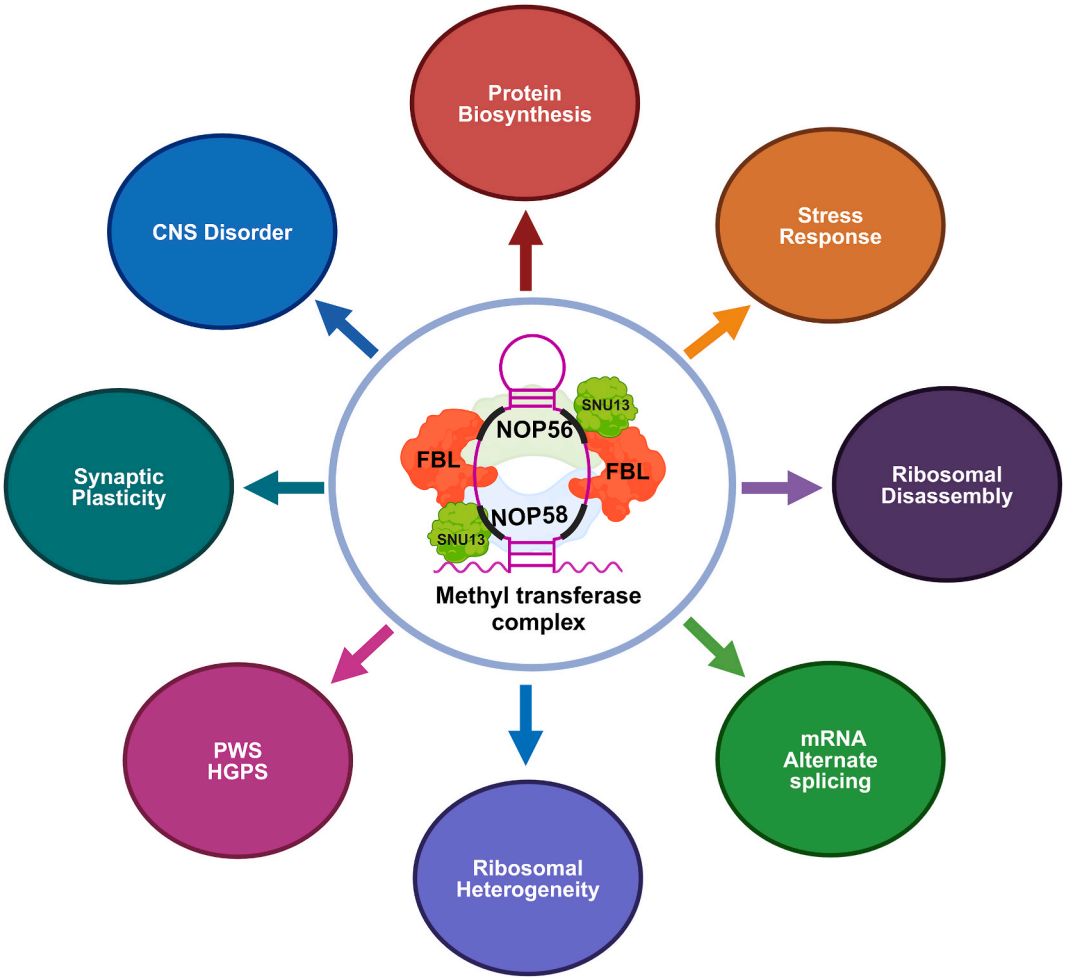


Fig. 2. Regulatory Impact of rRNA Modifications on Ribosome Function and Cellular Dynamics. This schematic illustrates the role of ribosomal RNA (rRNA) modifications in regulating various biological and pathological processes. Central to the figure is the enzymatic process of 2′-O-methylation of rRNA, catalyzed by the methyltransferase complex. This modification involves the methylation of the rRNA ribose sugar, representing a critical post-transcriptional change that significantly influences ribosome assembly and function. The figure highlights eight independent functional domains, each representing distinct biological processes influenced by rRNA methylation. Clockwise from the top, the domain labeled 'Protein Biosynthesis' emphasizes the essential role of ribosomes in translating mRNA into proteins. The 'Stress Response' domain reflects how rRNA modifications impact the cell's ability to respond to environmental stressors. 'Ribosomal Disassembly' demonstrates the effect of rRNA modifications on the formation and separation of ribosomal subunits. The 'mRNA Alternate Splicing' domain signifies how modified rRNA influences mRNA translation efficiency and specificity. In the lower half of the figure, 'Ribosomal Heterogeneity' represents the diversity in ribosome composition and function driven by differential rRNA modifications. The 'PWS (Prader-Willi Syndrome) and HGPS (Hutchinson-Gilford Progeria Syndrome)' domain highlights the broader impact of ribosomal activity on cellular health and behavior, with maladaptive protein synthesis potentially driven by aberrant 2′-O-methylation of rRNA. This maladaptive protein synthesis may contribute to the cellular dysfunctions observed in these syndromes, further emphasizing the influence of rRNA modifications on disease progression. 'Synaptic Plasticity' suggests that local ribosomal dysfunction due to altered rRNA methylation may play a significant role in neuropsychiatric disorders. Finally, the domain labeled 'CNS Disorders' points to a potential link between abnormal rRNA modifications and the development of neurological diseases. Overall, this figure underscores the complex interplay between rRNA modifications and cellular processes, highlighting the critical role of ribosome biogenesis and function in maintaining cellular health and influencing disease outcomes.

and impaired cellular functions, contributing to disease progression (Fig. 4B). Once the transcript is formed, many small nucleolar RNA (snoRNAs) start participating in modifying rRNA transcripts [30]. At the time of transcription elongation, assembly of 90S-sized precursor occurs, which requires the active participation of early ribosomal proteins (RPs) and ribosomal binding factors (RBFs), assisting in its co-transcriptional maturation [31–33]. Subsequently, an endonucleolytic cleavage of pre-RNA happens, which leads to the separation of pre-60S and pre-40S particles—followed by a series of independent maturation steps for each [34]. The 40S subunit, containing most ribosomal proteins (RPs), recruits ribosome binding factors (RBFs) and is then swiftly exported to the cytoplasm for final maturation [2]. The 60S subunit undergoes extensive rearrangements in the nucleus, incorporating 5S rRNA and facilitating the association and dissociation of RPs and RBFs. Once these modifications are complete, the 60S subunit is transported to the cytoplasm for its final maturation [2]. Both subunits in the cytoplasm assemble to form fully functional ribosomes capable of translation [1].

The following section discusses a detailed description of the rRNA molecules and their discerning roles in ribosome functioning. Additionally, molecular pathologies associated with their functional abnormalities have been outlined, focusing primarily on central nervous system (CNS) dysfunctions.

2. Constitutive function and modifications of rRNAs

As detailed previously, ribosome assembly relies fundamentally on the orchestration of ribosomal RNAs (rRNAs), serving as essential scaffolds that facilitate the incorporation of ribosomal proteins, thereby ensuring the proper folding and stability of the ribosomal complex [35]. Recent advancements have unveiled an interplay between rRNAs and various cellular pathways, shedding light on their involvement in crucial biological phenomena such as cell cycle regulation, cellular metabolism, and stress responses [36]. Moreover, rRNAs catalyze the critical process of peptide bond formation at the peptidyl transferase center (PTC) within the 28S rRNA, playing a central role in orchestrating the sequential elongation of nascent polypeptide chains during translation initiation and elongation [37,38]. Beyond their structural and catalytic roles, rRNAs regulate ribosome dynamics and conformational changes throughout the translation cycle [39]. These dynamic structural rearrangements, guided by interactions between rRNA domains, ribosomal proteins, and translation factors, precisely position mRNA and tRNA molecules within the ribosome, facilitating accurate decoding of genetic information and synthesizing functional proteins [40].

rRNAs contribute to translation fidelity by participating in quality control mechanisms that monitor the translational process, identifying and eliminating aberrant translation products to maintain cellular integrity and homeostasis [41]. Furthermore, rRNAs are emerging as critical regulators of gene expression and cellular function [42]. As mentioned previously, modifications of rRNA nucleotides, such as methylation and pseudouridylation, can modulate ribosome activity and mRNA translation rates, exerting significant influence over the expression of specific genes in response to developmental cues, environmental stimuli, or cellular stress [43]. Fig. 2 illustrates the regulatory role of 2′-O-methylation of rRNA in modulating ribosomal function and its impact on cellular dynamics. The figure highlights eight key functional domains influenced by this modification, including protein biosynthesis, stress response, ribosomal heterogeneity, and CNS disorders. It emphasizes how aberrant rRNA methylation, particularly in conditions like Prader-Willi Syndrome (PWS) and Hutchinson-Gilford Progeria Syndrome (HGPS), leads to maladaptive protein synthesis, contributing to disease pathology.

According to physiological needs, variations in rRNA sequence and structure among different ribosome isoforms or cell types confer functional specialization, enabling cells to fine-tune translational control [44]. Interactions between rRNAs and a diverse array of non-coding RNAs (ncRNAs) and regulatory proteins further expand the functional repertoire of rRNAs in mammalian cells. These interactions occur within the ribosome and the surrounding cellular environment, where rRNAs serve as platforms for assembling RNP complexes involved in RNA processing, localization, or degradation [45]. Additionally, specific RNA-binding proteins can bind to rRNA sequences or structural motifs to regulate ribosome biogenesis, translation initiation, or mRNA targeting, adding another layer of complexity to the regulatory networks governing gene expression [45,46].

Understanding the functions of rRNAs in mammalian cells is paramount for elucidating the molecular mechanisms underlying protein synthesis, cellular homeostasis, and disease pathology [47]. By unraveling the roles of rRNAs in diverse cellular processes, one can gain deeper insights into regulating gene expression, cellular differentiation, and disease progression, paving the way for developing novel therapeutic strategies targeting ribosomal function [48]. In addition to their pivotal roles in protein synthesis and gene expression regulation, rRNAs participate in various cellular processes, underscoring their significance in maintaining cellular homeostasis and responding to environmental cues [49,50]. One notable aspect of rRNA functionality is their involvement in cellular stress responses, particularly in environmental stressors that cells encounter [51]. When exposed to stressors such as oxidative stress, nutrient deprivation, or toxins, the expression and activity of rRNAs can be dynamically modulated to adapt to changing conditions [36]. This regulatory mechanism, the ribosomal stress response, is a complex cellular process that plays a vital role in maintaining cellular homeostasis under challenging circumstances [52]. The ribosomal stress response involves a series of signaling pathways that converge on the ribosome to regulate its assembly, activity, and turnover [52]. During ribosomal stress, cells may experience nucleolar stress, characterized by disruptions in ribosome biogenesis and nucleolar integrity. In response to nucleolar stress, cells activate signaling cascades involving key regulators such as the tumor suppressor protein p53, nucleophosmin (NPM1), and the ribosomal protein-MDM2 (Mouse double minute 2 homolog) complex. These regulators orchestrate a coordinated transcriptional and post-transcriptional response to restore ribosomal homeostasis [36,53,54]. They regulate rRNA synthesis and processing, ensuring the production of functional ribosomes while mitigating translational errors. Additionally, they prevent the accumulation of defective ribosomes that could compromise cellular functions and contribute to cellular dysfunction or disease pathogenesis [50].

The ribosomal stress response is particularly relevant in brain-related disorders, where disruptions in ribosomal function have been implicated in various disease conditions. For example, in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease,

and amyotrophic lateral sclerosis, environmental stressors can exacerbate ribosomal stress, leading to impaired protein synthesis and the accumulation of misfolded proteins [55,56]. These events contribute to neuronal dysfunction and cell death, critical features of these debilitating disorders. Psychiatric disorders like depression, anxiety, and schizophrenia are similarly linked to disturbances in protein synthesis and protein misfolding, which may be connected to ribosomal dysfunction exacerbated by environmental stressors [57,58]. Dysregulation of the ribosomal stress response in these disorders may impact synaptic plasticity, neurotransmitter signaling, and neuronal connectivity, contributing to the manifestation and progression of symptoms [49,50]. Thus, understanding the interplay between ribosomal stress, environmental factors, and brain-related disorders is essential for developing targeted therapeutic strategies to restore ribosomal homeostasis and alleviate disease-associated phenotypes. Continued research efforts aimed at elucidating the mechanisms underlying the ribosomal stress response in the context of CNS disorders will be crucial for advancing our understanding of these conditions and exploring druggable targets.

Emerging evidence suggests that rRNAs play central roles beyond the confines of the ribosome itself [59]. Recent studies have implicated rRNAs in regulating chromatin structure and epigenetic modifications, suggesting their involvement in broader aspects of genome regulation and cellular identity [60]. Through interactions with chromatin-modifying enzymes and transcription factors, rRNAs may influence gene expression programs and cellular differentiation trajectories, contributing to the establishment and maintenance of cell type-specific phenotypes [61]. Moreover, dysregulation of rRNA metabolism and function has been linked to various human diseases, including cancer, neurodegenerative disorders, and developmental abnormalities [62]. Mutations in genes encoding rRNA processing factors or ribosomal proteins can impair ribosome biogenesis, leading to ribosomopathies characterized by defective protein synthesis and cellular dysfunction [63,64]. Understanding the precise mechanisms by which rRNAs contribute to disease pathogenesis holds promise for developing targeted therapies to restore ribosomal homeostasis and mitigate disease-associated phenotypes [62].

In summary, the discussion above describes the multifaceted roles of rRNAs that extend far beyond their canonical functions in protein synthesis, encompassing diverse aspects of cellular physiology, stress responses, and disease pathogenesis. Moreover, epitranscriptomic modifications such as 2′-O-methylation play a crucial role in modulating the function of rRNAs, influencing overall ribosome activity and mRNA translation rates [9]. These modifications impact gene expression in response to developmental cues, environmental stimuli, or cellular stress, further emphasizing the dynamic nature of rRNA regulation [65]. Continued research efforts to unravel the complexities of rRNA biology promise to yield insights into fundamental cellular processes. They may offer new avenues for therapeutic intervention in human health and disease. Understanding the specific mechanisms through which rRNA and their modifications influence cellular physiology and disease pathology is critical. Acquiring in-depth knowledge regarding the targeted mechanisms may lead to developing therapeutic strategies that could help restore the ribosomal balance and alleviate the neuropsychiatric pathophysiology associated with ribosomal anomalies [43,66].

In the following section, we have highlighted some of the CNS-related roles of rRNAs associated with ribosomal dysfunctions. This section also explores how disturbances in rRNA function and modifications contribute to CNS disorders, providing insights into potential therapeutic targets for these conditions.

3. Biochemical frameworks of internal ribosome modifications

The non-coding RNAs undergo several types of chemical modifications in the cells. To date, 170 different types of RNA modifications have been reported [67]. These modifications are essential in RNA structure formation, splicing, transport, and polyadenylation. They also help in RNA-RNA and RNA-protein interactions. Transcript-level modifications are also expected for rRNA molecules. It has been generally noted that extensive rRNA modifications happen during their synthesis and processing inside the nucleolus, nucleus, or even outside the nuclear environment, i.e., cytoplasm. More specifically, ribosomal RNA undergoes three co and post-transcriptional modifications: methylation of ribose sugar (2′-O-Methylation), conversion of uridine into pseudouridine, and base modifications [68].

Base modification is categorized into acetylation, methylation, and aminocarboxypropylation. The most abundant co and post-transcriptional RNA modification is ribose methylation (Nm or 2′-O-Methylation) [13]. This modification adds a methyl group (CH3) to the ribose sugar's 2′ hydroxyl (OH) group. Ribose methylation occurs in all four nucleosides. Adding ribose methylation to rRNA co- and post-transcriptionally in eukaryotes is a complex process. It is facilitated by small nucleolar (sno) RNPs with the help of C/D box family snoRNAs, forming complexes known as C/D snoRNPs. FBL, or fibrillarin, is another critical component of this machinery, regulating rRNA transcription, precursor rRNA processing, and ribose modification. Its primary role is to catalyze ribose modifications in rRNA through the action of C/D-box snoRNPs, adding depth and complexity to our understanding of this process. More recently, internal ribose methylation has also been reported in mRNAs [69]. In yeast rRNA, 55 ribose-methylated sites are reported: 37 sites on 25S rRNA of a large subunit and 18 on 18S rRNA of a small subunit [70]. No ribose methylation has been reported in 5.8S and 5S RNA. However, in humans, there are 110 methylated sites across all rRNAs, including 67 in the 28S rRNA of the large subunit, 41 in the 18S rRNA of the small subunit, and two in the 5.8S rRNA. Table 1 shows a complete list of all 110 sites on different ribosomal RNA subunits based on the RiboMethSeq mapping data collected from various sources [71,72]. Recent advancements in molecular biology have started unveiling the multifaceted roles of 2′-O-Methylation of ribosomal RNA (rRNA) in brain functions, shedding light on its profound implications for a spectrum of neurodevelopmental, degenerative, and psychiatric disorders. Although initially acknowledged for its fundamental role in protein synthesis, 2′-O-Methylation is now recognized as a critical player in the intricate mechanisms governing neuronal health and contributing to the onset of various CNS disorders. This will be discussed in greater detail later in this review.

The second type of RNA modification is pseudouridylation, present in many RNAs, including rRNA, tRNA, snoRNA, miRNA, long

Table 1
2′-O-methylation sites in human rRNA.

Human 28s rRNA		
S. NO.	2′-O-methylation sites	SNORD
1	Am398	SNORD26
2	Am400	SNORD81
3	Gm1316	SNORD21
4	Am1323	SNORD126
5	Am1326	SNORD18, SNORD18A, SNORD18B, SNORD18C
6	Cm1340	SNORD104
7	Gm1522	SNORD2
8	Am1524	SNORD32A, SNORD32B, SNORD51
9	Am1534	SNORD77, SNORD80
10	Gm1625	SNORD80, SNORD118
11	Gm1760	SNORD73A
12	Am1871	SNORD38A, SNORD38B
13	Cm1881	SNORD48
14	Cm2351	SNORD24
15	Am2363	SNORD76
16	Gm2364	Unknown
17	Cm2365	SNORD24
18	Am2401	SNORD68
19	Um2415	SNORD143, SNORD144
20	Cm2422	SNORD5
21	Gm2424	SNORD6
22	Am2787	SNORD99
23	Cm2804	SNORD55
24	Am2815	SNORD95
25	Cm2824	SNORD95
26	Um2837	SNORD34
27	Cm2861	SNORD50A, SNORD50B
28	Gm2876	SNORD50A, SNORD50B
29	Gm3627	SNORD31
30	Cm3701	SNORD88, SNORD88A, SNORD88B, SNORD88C
31	Am3718	SNORD37
32	Am3724	SNORD36C
33	Gm3744	SNORD87
34	Am3760	SNORD46
35	Am3785	SNORD15A, SNORD15B
36	Gm3792	SNORD15A, SNORD15B
37	Cm3808	SNORD10
38	Ψm3818	SNORD17
39	Am3825	SNORD30
40	Am3830	SNORD79
41	Cm3841	SNORD74
42	Am3867	SNORD92
43	Cm3869	SNORD53, SNORD53, SNORD92
44	Cm3887	SNORD47
45	Gm3899	SNORD12, SNORD12B
46	Um3925	SNORD52
47	Gm3944	SNORD111, SNORD111B
48	Gm4042	SNORD102
49	Cm4054	SNORD75
50	Gm4196	SNORD31
51	Um4227	Unknown
52	Gm4228	SNORD58A, SNORD58B, SNORD58C
53	Um4306	SNORD41
54	Gm4370	SNORD60
55	Gm4392	SNORD1A, SNORD1B, SNORD1C
56	Cm4456	SNORD49A, SNORD49B
57	Gm4494	SNORD69
58	Um4498	SNORD62A, SNORD62B
59	Gm4499	SNORD75
60	Am4523	SNORD29
61	Cm4536	SNORD35A, SNORD35B
62	Am4571	SNORD63
63	Am4590	SNORD119
64	Gm4618	SNORD91A, SNORD91B
65	Um4620	SNORD72
66	Gm4623	SNORD78
67	Gm4637	SNORD1211, SNORD121B

Human 18s rRNA		
S. NO.	2′-O-methylation sites	SNORD
1	Am27	SNORD27
2	Am99	SNORD57
3	Um116	SNORD42A, SNORD42B
4	Um121	SNORD4A, SNORD4B
5	Am159	SNORD45A, SNORD45C
6	Am166	SNORD44
7	Um172	SNORD45A, SNORD45B
8	Cm174	SNORD45C
9	Um354	SNORD90
10	Um428	SNORD68
11	Gm436	SNORD100
12	Cm462	SNORD14, SNORD14A, SNORD14B, SNORD14C, SNORD14D, SNORD14E
13	Am468	SNORD83A
14	Am484	SNORD16
15	Gm509	SNORD11, SNORD11B
16	Am512	SNORD70
17	Cm517	SNORD56, SNORD56B
18	Am576	SNORD93
19	Am590	SNORD62A, SNORD62B
20	Gm601	SNORD85, SNORD103A, SNORD103B
21	Um627	SNORD65
22	Gm644	SNORD54
23	Am668	SNORD36, SNORD36A, SNORD36B
24	Gm683	SNORD19, SNORD19B
25	Cm797	SNORDZL107
26	Um799	SNORD105, SNORD105B
27	Gm867	SNORD98
28	Am1031	SNORD59A, SNORD59B
29	Ψm1232	SNORD103
30	Cm1272	SNORD66
31	Um1288	SNORD110
32	Ψm1326	SNORD33
33	Gm1328	SNORD32A, SNORD32B
34	Am1383	SNORD30
35	Cm1391	SNORD28
36	Um1442	SNORD61
37	Gm1447	SNORD127
38	Gm1490	SNORD25
39	Am1678	SNORD82
40	Cm1703	SNORD43
41	Um1804	SNORD20

Human 5.8s rRNA		
S. NO.	2′-O-methylation sites	SNORD
1	Um14	SNORD71
2	Gm75	SNORD96A, SNORD96B

intergenic non-coding RNA, mRNA, and other miscellaneous RNAs. In this modification, the uracil base rotates 180°, which is attached to the C1 carbon of ribose sugar via a carbon-carbon bond rather than a nitrogen-carbon glycosidic bond. Pseudouridylation is carried out by guide RNA (H/ACA box snoRNPs) and stand-alone enzymes [73]. In rRNA, this methylation is carried out by the H/ACA box complex, which contains snoRNA and four proteins, namely DKC1 (dyskerin), glycine-arginine-rich protein 1 (GAR1), nonhistone protein 2 (NHP2), and nucleolar protein 10 (NOP10). Pseudouridine modifications usually happen within conserved functional domains, and these modifications are essential for ribosome biogenesis and their function in eukaryotes. More than 100 pseudouridylations have been reported in human rRNA types [74]. However, their occurrences are relatively lower in bacteria (36 sites in E. coli) and yeast (46 sites in S. cerevisiae) rRNA [75]. In the following sections, we will mainly discuss the internal ribose methylation of rRNA molecules and the intricate mechanisms associated with those changes.

4. snoRNA synthesis & role in ribose methylation

Small nucleolar RNAs (snoRNAs) play a pivotal role in the post-transcriptional modification of ribosomal RNA (rRNA), which is crucial for the optimal functionality of ribosomes. snoRNAs vary in length from 50 to 70 nucleotides in archaea [69] to approximately 70–120 nucleotides in humans [9], reflecting adaptations to different cellular requirements across species. In mammals, genes encoding snoRNAs are often embedded within the introns of both protein-coding and non-coding RNA genes [76]. Transcription of these genes by RNA polymerase II includes adding a 5' monomethyl guanosine cap, stabilizing the RNA and facilitating further processing [77]. These specialized RNAs are marked by specific, conserved sequences: duplicated C boxes (RUGAGA, where R

represents a purine) at the 5′ terminus and D boxes (CUGA) at the 3′ terminus, supplemented by additional C′ and D′ motifs [9]. These elements facilitate the recognition of snoRNAs and underscore their functional specificity within the cellular environment. The structural integrity of snoRNAs is bolstered by a K-turn motif, essential for their intracellular trafficking, reactivity, and stability. This structural feature enables snoRNAs to navigate through the cellular environment to their sites of action effectively. Following transcription, the assembly of snoRNA with ancillary protein components to form snoRNP (small nucleolar ribonucleoprotein) complexes runs through a meticulously orchestrated multistep process (Fig. 3). It begins with splicing the precursor snoRNA, followed by exonucleolytic trimming to refine the snoRNA structure [78]. Proteins associated with the C/D box snoRNP complex, such as fibrillarin, NOP56, and SNU13, shield snoRNAs from degradation and assist in their proper folding into functional kink-turn (k-turn) and kink-loop (k-loop) motifs. These structures are crucial as they enable snoRNAs to guide specific methylation processes on rRNA, which is essential for the accurate folding and functionality of ribosomes (Box 1).

The mature C/D box snoRNP complex, which includes SNU13, NOP56, NOP58, and Fibrillarin, is transported to the nucleoli via NOPP140 [79]. There, it performs 2′-O-methylation of rRNA, a modification pivotal for the ribosome's structural integrity and translational accuracy. Complementing the role of snoRNAs, long nucleolar-specific lncRNAs (LoNA) significantly contribute to ribosomal heterogeneity [80]. These lncRNAs orchestrate the modification and processing of pre-rRNA, recruiting snoRNAs and ribonucleoprotein complexes to perform site-specific modifications such as pseudouridylation and methylation. As discussed earlier, such

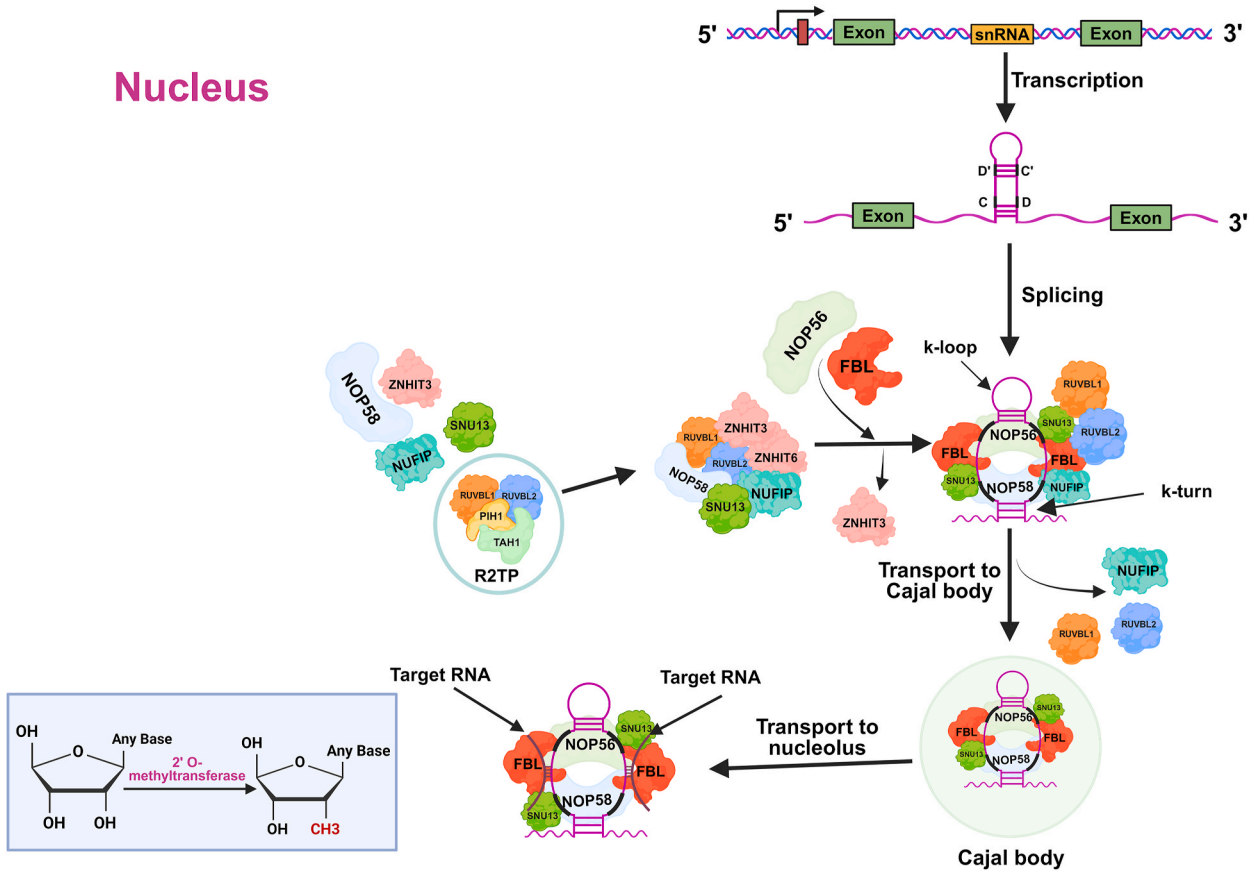


Fig. 3. C/D Box snoRNA Biogenesis in Human Cells. This figure delineates the pathway of C/D box small nucleolar RNA (snoRNA) biogenesis within human cells, illustrating the complex multistep process from gene transcription to the functional snoRNA involved in rRNA modification. The pathway begins with the transcription of C/D box snoRNA genes by RNA polymerase II (or III for some snoRNAs), typically found within the introns of host genes. After transcription, the pre-snoRNA is co-transcriptionally cleaved and liberated from its host intron by the spliceosome during pre-mRNA splicing. The emerging pre-snoRNA undergoes a series of maturation steps, including endo- and exonucleolytic trimming to form the mature C/D box snoRNA structure, characterized by the conserved C and D box motifs critical for function and stability. This mature snoRNA is then bound by specific core proteins, including fibrillarin, the methyltransferase responsible for catalyzing 2′-O-methylation of target rRNAs, to form a functional snoRNP complex. The figure also shows the transportation of the snoRNP to the nucleolus, where it guides the methylation of rRNA, contributing to the modification and maturation of ribosomal subunits. This biogenesis pathway is essential for the precise post-transcriptional modifications of rRNA, which are crucial for the proper assembly and function of ribosomes. The inset highlights the interactions between the snoRNA, core proteins, and rRNA, providing a close-up of the molecular mechanisms that drive rRNA modification. This biomolecular illustration emphasizes the intricate regulatory mechanisms of ribosomal biogenesis and the pivotal role of C/D box snoRNAs in cellular homeostasis and gene expression.

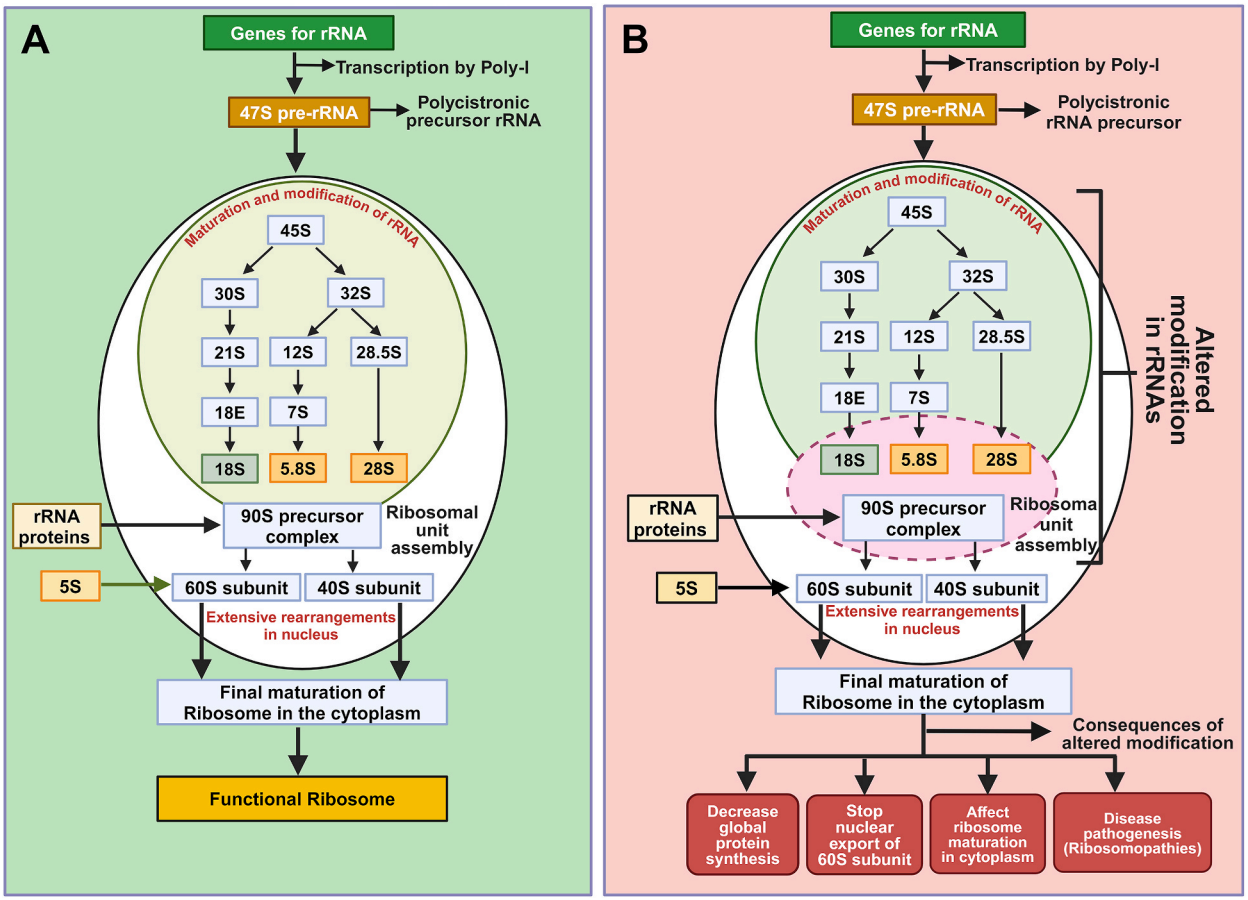


Fig. 4. From Normality to Abnormality: The Altered Fate of Ribosome Biosynthesis. The flow diagram illustrates the steps involved in normal ribosome biosynthesis and the consequences of altered ribosome biogenesis. In Fig. 4A, the schematic diagram depicts the process of normal ribosome biogenesis under typical cellular conditions, highlighting several key steps susceptible to internal ribosomal modifications, including 2′-O-methylation. The process begins with the transcription of a single pre-rRNA precursor in the nucleus, which contains the 28S, 18S, and 5.8S rRNA sequences. This precursor undergoes a series of cleavage events, followed by the addition of critical modifications, such as 2′-O-methylation. Next, the 5S rRNA and ribosomal proteins assemble to form the pre-ribosomal unit. This pre-ribosomal complex undergoes extensive rearrangements within the nucleus and is subsequently transported to the cytoplasm, where it undergoes final maturation into fully functional ribosomes. In Fig. 4B, the flow diagram outlines the effects of altered 2′-O-methylation of rRNA and its impact on ribosome biogenesis. Aberrant modifications disrupt the ribosomal rearrangement process in the nucleus, leading to the production of nonfunctional ribosomes. Under stress conditions, these altered rRNA modifications result in a significant reduction in global protein synthesis, hinder the nuclear export of the 60S ribosomal subunit, and impair the maturation of ribosomes in the cytoplasm. This dysfunction contributes to disease pathogenesis by compromising normal cellular functions, emphasizing the critical role that proper rRNA modifications play in maintaining ribosomal integrity and overall cellular health.

modifications provide ribosomes with the structural and functional versatility necessary for the selective translation of mRNA, thus ensuring the precision of protein synthesis (Box 2). Additionally, certain snoRNAs, termed SNORDs, have unique RNA polymerase II promoters [88] and function similarly to RNA chaperones [83]. They facilitate pre-rRNA processing into its mature forms (28s, 18s, 5.8s rRNA), which are foundational for ribosome assembly and translational activity [83]. While snoRNA-guided methylations typically target specific nucleotides, demonstrating the precision of these molecular guides, some snoRNAs can modify multiple positions on the rRNA, illustrating the complexity and specificity of their role in cellular physiology [9]. This continuous narrative emphasizes the integral roles of snoRNAs and lncRNAs in ribosome biogenesis and functionality, highlighting the sophisticated regulatory mechanisms underpinning protein synthesis in eukaryotic cells.

5. Role of fibrillarin (FBL) in ribose methylation

FBL is a small 34 kDa highly conserved nucleolar protein. It is found in a dense fibrillar center in the nucleus and, thus, called fibrillarin. FBL protein sequence and functions are conserved throughout evolution from archaea to humans [89,90]. It contains three structural domains: an N terminal glycine and arginine-rich domain (GAR, aa 180), a central domain (~90aa) with RNA binding capacity, and a C terminal α-helical domain (~33 aa). These three domains are separated by two short spacer sequences, Sp1 and Sp2

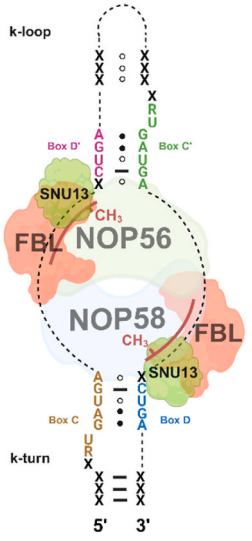
Box 1
Functional importance of C/D box snoRNA in rRNA modification [81,84–87].

Box 1: Functional importance of C/D box snoRNA in rRNA modification

C/D box small nucleolar RNAs (snoRNAs) are pivotal in modifying ribosomal RNA (rRNA). These small, non-coding RNAs are essential components of the ribonucleoprotein complexes that drive site-specific rRNA methylation, which is a critical step in the maturation of functional ribosomes. Each C/D box snoRNA contains conserved sequence motifs known as C (RUGAUGA) and D (CUGA) boxes and C' and D' boxes, which are intermediate but similarly essential motifs [9]. These elements serve as binding sites for proteins like fibrillarin, Nop56, Nop58, and SNU13, forming a small nucleolar ribonucleoprotein (snoRNP) [81]. In this complex, fibrillarin acts as a methyltransferase that catalyzes the 2'-O-ribose methylation of specific nucleotides in rRNA [82]. The unique feature of C/D box snoRNAs is their ability to guide methylation. They contain short regions complementary to the target rRNA sequences, allowing them to bind specifically to rRNA.

Once hybridized, the snoRNP directs fibrillarin to methylate the nucleotide at the designated position [83]. This modification stabilizes the rRNA structure and facilitates proper folding, which is vital for efficient ribosome assembly and function [84]. The modifications facilitated by C/D box snoRNAs are essential for ribosomal fidelity and specialization. They enhance the structural stability of rRNA, ensuring the proper formation of the ribosomal subunits that drive translation [85]. Additionally, these modifications can influence ribosome heterogeneity, leading to ribosome specialization in translating particular mRNA subsets [43]. This specialization can have essential implications in different tissues or conditions, allowing adaptive protein synthesis.

Furthermore, C/D box snoRNAs have emerging roles beyond rRNA methylation. Recent studies suggest they may participate in modifying other RNAs or even act independently in regulating cellular processes [86]. Mutations or dysregulation of C/D box snoRNAs are implicated in various human diseases, including cancer, where altered ribosome function leads to cellular growth and survival changes [87]. In conclusion, C/D box snoRNAs are integral to rRNA modification and ribosome maturation. Their precise function in guiding site-specific methylation underscores their importance in protein synthesis, cellular adaptation, and disease. Understanding their mechanisms opens doors for potential therapeutic interventions targeting snoRNA-related pathways.



(~50 amino acids). The methyltransferase activity is attributed to the RNA binding central and C terminal domains of the FBL protein [90]. In addition to its role in nucleolar dynamics, FBL is an independently acting s-adenosine methionine (SAM)-dependent methyltransferase that can methylate RNAs and proteins [92]. However, the primary function of the FBL protein is to catalyze the ribose modifications in rRNA with the help of C/D-box snoRNPs. Besides the methylation modification role, the role of FBL in ribosomal RNA biosynthesis also involves its regulation of transcription and processing of rRNA transcripts [82,93]. FBL is a critical component that governs the rRNA transcription, precursor rRNA processing, and ribose modification of rRNA. If the expression of FBL protein changes, it affects the course of all the above-mentioned cellular processes (Box 3).

The discussion above suggests that FBL is an essential nucleolar protein involved in rRNA modification, transcription regulation, and processing of precursor rRNA. Its highly conserved structure and invaluable roles highlight its significance in maintaining cellular function and stability through ribosomal RNA health.

6. Role of rRNAs in regulating CNS functions and disorders

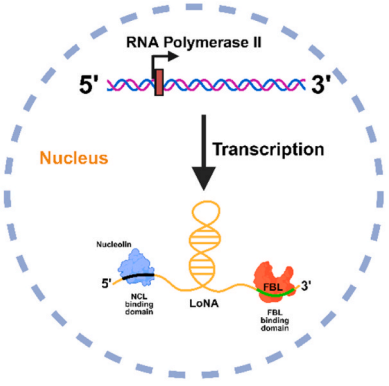
Recent research has illuminated novel roles of rRNAs in neuronal functions and CNS disorders, expanding our understanding of the molecular mechanisms underlying these complex conditions [103]. One exciting area of investigation involves the regulation of

Box 2
Regulation of rRNA production and altered ribosomal heterogeneity through nucleolar specific lncRNA (LoNA) [91].

Box 2: Regulation of rRNA production and altered ribosomal heterogeneity through nucleolar specific lncRNA (LoNA)

Nucleolar-specific long non-coding RNAs (lncRNAs) have emerged as crucial regulators of ribosomal RNA (rRNA) production and diversity, pivotal in ribosome assembly and function [91]. These lncRNAs, including NEAT1 and PWRN1, are integral to the complex processes of rRNA transcription, processing, and modification within the nucleolus, which serves as the cellular hub for ribosome synthesis. In eukaryotic cells, the nucleolus orchestrates rRNA transcription from ribosomal DNA (rDNA) templates and guides the processing of precursor rRNA into functional ribosomal subunits. By interacting with RNA polymerase I and various regulatory proteins, nucleolar lncRNAs help modulate the transcription of rDNA, precisely controlling pre-rRNA production. Additionally, these lncRNAs direct the localization of transcription factors and regulatory proteins to specific rDNA regions, thereby influencing the rate and efficiency of rRNA synthesis.

Moreover, nucleolar-specific lncRNAs also shape rRNA heterogeneity by guiding the modification and processing of pre-rRNA. They recruit small nucleolar RNAs (snoRNAs) and ribonucleoprotein complexes necessary for site-specific modifications such as pseudouridylation and methylation. These modifications endow ribosomes with the structural and functional versatility needed to translate specific mRNA subsets, thus ensuring the precision of protein synthesis precision. LoNA (long nucleolar-specific lncRNA) exemplifies the regulatory capabilities of these molecules. Its five ′ region binds to nucleolin, inhibiting rRNA transcription, while its snoRNA-like three ′ region interacts with fibrillarin to suppress rRNA methylation. This dual-action mechanism reduces overall rRNA production and alters ribosomal heterogeneity. The mature rRNAs (28S, 18S, and 5.8S) are markedly diminished when LoNA levels rise, while the transcription of 5S rRNA remains unaffected. By influencing the chromatin state of rDNA promoter regions and reducing the binding of key transcription factors like UBF, LoNA efficiently suppresses rRNA synthesis. Although LoNA is not conserved across species, the human lncRNA RP11-517C16.2 possesses similar binding sites for nucleolin and fibrillarin, hinting at a conserved functional mechanism. The depletion of nucleolin disrupts RNA polymerase I activity and inhibits rDNA transcription, underscoring the importance of this interaction. Nucleolar-specific lncRNAs regulate rRNA transcription, processing, and modification, underpinning ribosome assembly and function [80]. Their influence on protein synthesis efficiency and adaptability advances our understanding of basic cellular biology and provides valuable insights into nucleolar-associated diseases like ribosomopathies.



synaptic plasticity and neuronal connectivity by rRNAs [104]. Synaptic plasticity, the ability of synapses to strengthen or weaken over time in response to activity, is fundamental to learning and memory processes in the brain [105]. Emerging evidence suggests that rRNAs play an essential role in regulating synaptic plasticity by modulating the local translation of synaptic proteins at dendritic spines, specialized structures where synapses form [103]. Through dynamic interactions with RNA-binding proteins and regulatory RNAs, rRNAs contribute to precisely controlling protein synthesis at synapses, influencing synaptic strength and neuronal circuitry [106]. Furthermore, dysregulation of rRNA metabolism and ribosome function has been implicated in various psychiatric disorders, including schizophrenia, bipolar disorder, and major depressive disorder. Genome-wide association studies (GWAS) have identified genetic variants in rRNA genes and ribosomal protein genes associated with increased susceptibility to these disorders, highlighting the importance of ribosomal dysfunction in their pathogenesis [107,108]. Aberrant rRNA processing, ribosome biogenesis, and translation control mechanisms have been observed in postmortem brain and cellular models of psychiatric disorders, suggesting a link between disrupted ribosomal function and neuronal dysfunction [29]. Moreover, alterations in rRNA modifications have emerged as potential contributors to psychiatric disorders [109]. RNA modifications, such as methylation and pseudouridylation, modulate ribosome activity and translational efficiency, thereby influencing the expression of synaptic proteins and neuronal signaling pathways [110,111]. Dysregulated rRNA modifications have been implicated in synaptic dysfunction, impaired neuronal plasticity, and aberrant neurotransmission, hallmark features of psychiatric disorders [111]. Indeed, recent research has unveiled the significance of rRNA epitranscriptomic changes in the context of neuronal functions and psychiatric disorders. Epitranscriptomic modifications, such as

Box 3
FBL- a key player for ribosome biogenesis and its association with neurological and psychiatric disorder [95,98–101].

Box 3: FBL- a key player for ribosome biogenesis and its association with neurological and psychiatric disorder

Fibrillarin is a nucleolar protein known for its essential role in ribosomal RNA (rRNA) biosynthesis and modifications. This highly conserved protein is present across eukaryotes and archaea, emphasizing its fundamental importance in cellular biology[89,90]. It functions primarily as a critical component of small nucleolar ribonucleoproteins (snoRNPs), which are involved in the chemical modification of rRNA, an essential step for ribosome maturation. In rRNA biosynthesis, fibrillarin is crucial during the early stages of processing [94]. It is closely associated with the snoRNAs that guide chemical modifications, such as methylation and pseudouridylation, at specific nucleotides in the rRNA sequence. Fibrillarin functions as the catalytic methyltransferase within snoRNP complexes, adding methyl groups to the 2'-hydroxyl position of ribose sugars[90]. This modification stabilizes rRNA structure, ensures accurate folding, and supports the formation of functional ribosomal subunits. In addition to guiding methylation, fibrillarin plays an indirect role in pseudouridylation, another significant rRNA modification. It is believed to assist in snoRNA stabilization, enhancing their ability to guide pseudouridine synthases to the correct rRNA sites. These modifications are crucial for forming functional ribosomal subunits and practical protein synthesis. Fibrillarin's influence extends beyond its catalytic activity. It also participates in organizing the nucleolus and rRNA gene transcription[95]. By binding to specific nucleolar organizer regions, fibrillarin facilitates the proper localization of other snoRNPs and transcription factors, thereby helping to establish nucleolar structure and function. Given its pivotal role in ribosome biogenesis and nucleolar structure, fibrillarin is essential for cell survival and growth[11,94,96,97]. Its dysfunction is implicated in various diseases, particularly cancer[98-101] and neurodegenerative disorders, where aberrant ribosome biogenesis leads to uncontrolled cell proliferation or neuronal damage[102]. Therefore, studying fibrillarin provides valuable insights into the fundamental processes of ribosomal assembly, protein synthesis, and disease mechanisms. Understanding its precise molecular functions can open avenues for therapeutic interventions targeting ribosomal biogenesis pathways.

methylation and pseudouridylation, which occur post-transcriptionally on rRNA molecules, have emerged as critical regulators of the brain's ribosome function and translational control. Studies have shown that dysregulation of rRNA epitranscriptomic modifications can impact ribosome activity, alter mRNA translation rates, and perturb protein synthesis dynamics, ultimately influencing synaptic plasticity and neuronal function [65,112]. For example, aberrant chemical modifications on specific rRNA residues have been associated with altered ribosome function and impaired translation fidelity, leading to synaptic dysfunction and cognitive deficits observed in psychiatric disorders [113]. Furthermore, disruptions in the enzymes responsible for rRNA modification, such as methyltransferases and pseudouridine synthases, have been implicated in the pathogenesis of neurological and psychiatric conditions [114]. Genetic mutations or dysregulation of these enzymes can result in aberrant rRNA modifications, leading to defects in ribosome biogenesis, translation dysregulation, and synaptic dysfunction [43,62]. Moreover, emerging evidence suggests that environmental factors, including stress and exposure to psychotropic drugs, can influence rRNA epitranscriptomic modifications in the brain [49]. These environmental cues may alter the activity of rRNA-modifying enzymes, leading to changes in ribosome function and translational output, thereby contributing to the pathophysiology of psychiatric disorders [115]. Understanding the role of rRNA epitranscriptomic changes in neuronal functions and psychiatric disorders offers new insights into the molecular mechanisms underlying these complex conditions. Targeting epitranscriptomic pathways associated with rRNA modifications may represent a promising therapeutic approach for restoring synaptic plasticity, rebalancing neuronal circuits, and ameliorating symptoms of psychiatric illness. Additionally, investigating the interplay between genetic, epigenetic, and environmental factors in modulating rRNA epitranscriptomic changes may provide valuable clues for developing personalized treatment strategies. Furthermore, unraveling the roles of rRNAs in neuronal functions and psychiatric disorders offers new avenues for therapeutic intervention. Targeting rRNA metabolism, ribosome biogenesis, or translation control mechanisms may represent novel strategies for restoring synaptic plasticity, rebalancing neuronal circuits, and ameliorating symptoms of psychiatric illness. Furthermore, elucidating the molecular mechanisms underlying ribosomal dysfunction in psychiatric disorders may facilitate the development of biomarkers for early diagnosis and personalized treatment approaches [116].

In summary, rRNAs play multifaceted roles in regulating neuronal functions and synaptic plasticity, which has implications for neuropsychiatric disorders. Advanced insights into the molecular mechanisms governing rRNA-mediated synaptic regulation offer

promising opportunities for understanding disease pathogenesis and developing innovative therapeutic interventions.

7. From RNA modification to proteomic instability: unraveling CNS disorders through 2′-O-methylation

Recent understanding of 2′-O-ribose methylation has emerged as a key mechanism in brain function [109]. It has been suggested that this unique ribosomal RNA modification can potentially influence protein synthesis dynamics, proteostasis, stress responses, synaptic plasticity, and neuroinflammatory processes within the brain [9,117–119]. These multifaceted roles of 2′-O-ribose methylation collectively provide a comprehensive framework for understanding disease mechanisms and simultaneously open up an opportunity to develop targeted therapies for complex neurodevelopmental, neurodegenerative, and neuropsychiatric conditions [120,121].

A critical aspect of 2′-O-Methylation involves its influence on proteostasis, the cellular process responsible for maintaining the proper folding and functionality of proteins [118,122,123]. In neurons, precise protein synthesis is essential for cellular function and survival, making robust proteostasis mechanisms crucial [117]. Ribosomes, guided by rRNA modifications like 2′-O-Methylation, ensure accurate protein synthesis by enhancing the stability and functional integrity of rRNA [40]. This modification optimizes the fidelity of protein folding processes, ensuring that newly synthesized proteins adopt their correct three-dimensional structures [124,125]. Disruptions in 2′-O-Methylation can compromise these processes, leading to the production of misfolded or dysfunctional proteins. When neurons are exposed to continuous stimuli they need to adapt. These adaptations are important for the neural physiology and survival of the neurons. For this, neurons must rely on ribosome biogenesis, and proper 2′-O-methylation of rRNA is necessary for the ribosome biogenesis. Alteration in this step could induce neuroinflammation. For example, 2′-O-modification is associated with neurodegenerative disorder, in which Tau protein plays a key role in disease pathogenesis. Evidence shows that Tau protein is re-localized under glutamate-induced cellular stress, resulting in redistribution of FBL and reduced synthesis of pre-rRNA. This redistribution impacts 2′-O-methylation and causes neuroinflammation [10]. These abnormal proteins may accumulate and form toxic aggregates, characteristic of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [126]. To better understand the relationship between 2′-O-ribose methylation and neurological disorders, Table 2 summarizes key CNS conditions linked to this modification [12,127–129]. The table outlines specific disorders and includes references that detail the functional and mechanistic roles of 2′-O-methylation in each condition. This compilation offers a structured and well-supported overview of the associations discussed, helping to consolidate the evidence and reduce the speculative nature of the manuscript. Thus, RNA modifications are pivotal in preserving neuronal proteostasis and are implicated in the molecular pathology of these debilitating conditions [130].

2′-O-Methylation also plays a crucial role in regulating stress responses within the brain. Stress, whether acute or chronic, triggers molecular cascades that profoundly impact neuronal function. Studies indicate that rRNA methylation patterns respond to stressors, influencing the efficiency and accuracy of protein synthesis under these conditions [131,132]. Stress-induced alterations in rRNA methylation may affect the synthesis of stress-responsive proteins crucial for neuronal adaptation and resilience [133]. Dysregulation of these processes has been linked to the development of stress-related mental disorders, including anxiety disorders and depression, where disruptions in protein synthesis dynamics contribute to synaptic dysfunction and impaired neuronal plasticity [133].

Additionally, the link between 2′-O-Methylation and neuroinflammation adds another layer to its role in CNS disorders [49,134]. Neuroinflammation, characterized by immune activation within the central nervous system, is implicated in various brain disorders [135–137]. Recent studies suggest that rRNA methylation influences neuroinflammatory pathways, modulating immune responses and contributing to disease progression [138]. Dysregulation of rRNA methylation may exacerbate neuroinflammatory processes, leading to chronic inflammation and neuronal damage observed in conditions including neurodegenerative diseases.

In summary, 2′-O-methylation plays an essential role in shaping ribosomal function and offers a scope to understand its potential implications for unraveling the pathophysiology of neurological diseases. Insights gained from studying this RNA modification could offer new avenues for therapeutic strategies targeting ribosomal dysfunction and associated neuropathological conditions, paving the way for advances in precision medicine and therapeutic interventions.

8. Association of FBL with CNS disorders

In recent years, numerous studies have demonstrated that abnormal expression of FBL is linked to various diseases, including aging and early developmental disorders [139]. FBL has been suggested to play a critical role in regulating nucleolar size, which has been

Table 2
Summary of the functional and mechanistic links between 2′-O-ribose methylation and neurological disorders.

S. no.	Disease	Reason	Function	Reference
1	Prader Willi Syndrome	Deletion of SNORD115 and SNORD116 imprinted gene clusters present on chromosome region 15q11-q13	PWS encoded SNORDs involved in the synthesis and function of ribosomes in neuronal tissue	Cavaille et al. [12]
2	Fragile X syndrome	Loss of FMRP protein	FMRP recognizes ribosomes carrying specific methylation patterns on rRNA.	D'Souza et al. [127]
3	Huntington disease	Increased level of SNORD13	SNORD13 is involved in the processing of rRNA	Romano et al. [129]
4	LLD or Parkinson	Mutation in SNORD118	SNORD18 involved in ribosome biogenesis	Jenkinson et al. [128]

connected to lifespan in multicellular organisms. For instance, nucleolar activity and ribosome biogenesis led to elevated global protein synthesis in fibroblasts from patients with Hutchinson-Gilford syndrome, a premature aging condition. Additionally, nucleolar size and ribosomal production correlate with age in healthy humans. These findings highlight the importance of FBL in maintaining cellular function and health through its influence on nucleolar size and activity [140]. In a significant study, investigators have explored the regulation of nucleolar size in Caenorhabditis elegans, a lower metazoan, with a particular focus on the role of FBL in nucleolar size determination. The study uncovered a complex network involving microRNA let-7, the translation repressor NCL-1, and the FBL that governed nucleolar size. NCL-1 suppressed FBL translation with the aid of RNA-binding proteins PUF and NOS, while let-7 inhibited NCL-1 expression by targeting its 3′ UTR. This precise regulation tightly controlled the abundance of FBL, which was intricately linked to nucleolar size. The findings underscore the critical role of FBL in nucleolar size determination, thereby highlighting its significance in this process [141]. In the context of FBL, it has been observed that long-lived animals exhibit a reduction in FBL expression, smaller nuclei, and a decrease in ribosomal proteins and rRNA, which collectively suggest a lower rate of ribosome synthesis and protein production. This reduction in ribosomal biogenesis contributes to longevity by minimizing cellular stress and damage associated with protein synthesis. Supporting this, human muscle biopsy samples from individuals who have undergone dietary restriction—a regimen known to extend lifespan also demonstrate smaller nucleoli, indicating lower ribosome production similar to that seen in long-lived species. These findings implicate a downregulation of FBL and associated ribosomal components as a cellular hallmark of longevity, suggesting that reduced ribosomal activity may be a conserved mechanism underlying increased lifespan [142]. In a separate study, the researcher investigated the role of FBL in early embryonic development by devising a gene trap screening system using embryonic stem cells, which resulted in an insertion mutation in the FBL gene. By transferring the targeted FBL allele through the mice germ line, heterozygous animals were created. Heterozygous animals showed a reduction in FBL protein, but homozygous animals for mutation were inviable, and massive apoptosis was seen in early FBL embryos. These results showed that FBL is essential for development [94]. Other groups studied the role of FBL in the early development of Xenopus laevis. In developing embryos, they reported FBL transcript enrichment in neural plates, neural crest cells (NCC), and NCC derivatives. FBL knockdown causes p-53-dependent apoptosis of NCCs and morphological defects in the eyes and craniofacial skeleton. As we have discussed, FBL is required for efficient pre-rRNA processing and 18S rRNA production, which may partly explain the early developmental defects seen in the Xenopus experiment [96]. Since FBL is a key factor for 2′-O-methylation of rRNA, any changes in its expression levels can significantly impact the translation process. A study highlighted this, where the knockdown of the FBL protein altered the capacity of ribosomes to initiate translation, demonstrating the crucial role of FBL in maintaining the efficiency and accuracy of protein synthesis [11]. FBL is also required for embryonic development. Bouffard and colleagues showed that optic tectum and eyes are severely affected by low levels of FBL, and morphogenesis defects are associated with impaired neural differentiation and massive apoptosis [102]. The importance of FBL is highlighted in several other studies that show its critical role in maintaining nuclear shape, cell survival, and early development [94,97].

9. Association of snoRNAs with CNS disorders

Owing to the critical influence of snoRNAs in protein synthesis, any aberrant expression and depletion of snoRNAs in mammalian cells can impact both ribosome biogenesis and translational activity. This aberrant expression and depletion can occur through RNA sequences, transcription, and processing changes. If snoRNAs fail to perform their function accurately, it can result in a wide range of human diseases, including neurodevelopmental disorders. This has been studied in zebrafish, where the expression of snoRNAs (U26, U44, and U78) was suppressed by inhibiting snoRNA precursor processing or disrupting the host gene silencing. U26 deficiency resulted in defective morphogenesis and embryonic lethality. In the case of U44 deficiency, zebrafish exhibited delayed eye pigmentation and severe brain hypoplasia. Similarly, U78 deficiency led to incomplete yolk sac extension and reduced body size. These studies demonstrated that decreased expression of these snoRNAs caused embryonic lethality and severe morphological defects in zebrafish [143]. In other studies, C/D box snoRNAs are involved in neurodevelopmental and neuropsychiatric disorders. Interestingly, the role of C/D box snoRNA has been highlighted in Prader-Willi syndrome (PWS), which is a complex neurodevelopmental human disease and linked to SNORD115 and SNORD116 imprinted gene clusters present on chromosome region 15q11-q13 (the SNURF-SNRPN domain). Initially, snoRNA C/D box HBII-52 (SNORD115) and HBII 85 (SNORD116) were detected on the chromosome region 15q11-q13 with 48 copies of SNORD115 and 29 copies of SNORD116 genes, respectively. Later, it was suggested that the etiology of PWS is associated with altered levels of snoRNA 115, snoRNA116, and large deletion of related genes. In a separate study, snoRNA115 was also found to play a key role in post-transcriptional processing of serotonin receptor (5-HT2C) pre-mRNA transcript [12]. The role of the serotonin receptor (5-HT2C) in major depressive disorder (MDD) is well known. One study reported genome-wide methylation differences between the monozygotic twins discordant for schizophrenia (SCZ). Specifically, SNORD115 and SNORD116 were differentially methylated in the twins with SCZ compared to their unaffected counterparts [144]. Studies have also reported significant alterations in snoRNAs within synaptosomes isolated from the prefrontal cortex (PFC) of individuals with SCZ. Notably, SNORD85 showed a 50 % decrease in SCZ synaptosomes. The most abundant 27-mer sequence (TTCACTGATGAGAGCATTGTTCTGAGC) of SNORD85 contains a C/D box and terminates four bases before the 3' end of the host snoRNA. This snoRNA is part of a novel class of small non-coding RNAs that are highly expressed in humans, especially in synaptosomes, and are significantly altered in psychiatric disorders [145]. Additionally, another study revealed changes in snoRNA expression in SCZ, identifying 343 snoRNAs expressed in both SCZ patients and controls, with 6 specifically expressed in SCZ. However, no significant differences in overall snoRNA expression levels were observed between SCZ patients and controls [146].

10. Conclusion, future directions, challenges and limitations

Mounting evidence shows the influence of impaired mRNA translation in numerous CNS brain disorders, and studies have found that translation malfunctionality can significantly contribute to the development of neurological and psychiatric diseases [147,148]. rRNAs play multifaceted roles in cellular physiology, stress responses, and disease pathogenesis by regulating protein translation, underscoring their significance as central players in biological processes. From their canonical functions in protein synthesis to their dynamic modulation through modifications like 2′-O-methylation, rRNAs are intricately involved in regulating gene function and cellular homeostasis [11,149]. Thus, defects in their synthesis, processing, and post-transcriptional modifications may negatively affect protein synthesis and subsequent biological functions. As we unravel the complexities of rRNA biology, future research should focus on elucidating the precise mechanisms underlying rRNA function and modification in health and disease. Additionally, it is crucial to understand at what stages rRNAs are dysfunctional and whether these are associated with altered synthesis of specific proteins or with dysregulation of guided snoRNAs. Two prominent factors, snoRNA and FBL, are involved in rRNA functions, and their modifications are associated with certain CNS disease conditions. A few studies report that snoRNAs can be associated with psychiatric illnesses; however, how they participate in these disorders is not yet understood [83]. Understanding how disturbances in rRNA regulation contribute to the pathogenesis of neurological and psychiatric disorders, such as Alzheimer's disease, Parkinson's disease, major depression, and schizophrenia, holds promise for identifying novel therapeutic targets.

While exploring the potential of targeting rRNA modifications and regulatory pathways for therapeutic intervention represents an exciting avenue for developing precision medicine approaches [150], it is important to acknowledge several potential challenges and limitations. First, the complexity of rRNA modifications and their interactions with multiple cellular pathways makes it difficult to target specific modifications without affecting other critical functions. Moreover, the risk of off-target effects when manipulating such essential processes in the ribosome could lead to unintended consequences, particularly given the ubiquitous role of ribosomes across different cell types. Translating findings from basic research into clinical applications will require overcoming these hurdles, as well as addressing the challenge of delivering targeted treatments to specific regions of the brain affected by disease [151].

Advances in technologies such as single-cell sequencing, CRISPR-based gene editing, and high-resolution imaging techniques hold promise for researchers to dissect the critical roles of rRNAs with unprecedented detail. However, translating these discoveries into clinical therapies will need to account for the difficulty of targeting rRNA modifications in a way that is both specific and safe for patients. Interdisciplinary collaborations between molecular biologists, neuroscientists, clinicians, and computational biologists will be crucial to driving innovation and accelerating progress in this field while also navigating the complexities of developing targeted rRNA-based therapies.

By restoring ribosomal homeostasis and mitigating disease-associated phenotypes, we can facilitate more effective treatments and improved outcomes for patients with neurological and psychiatric disorders. The outlook for rRNA research is promising, but carefully navigating these challenges will be essential to translating these advances into therapeutic success. In conclusion, studying rRNA biology represents a frontier in biomedical research, offering opportunities to uncover fundamental cellular processes and develop innovative therapeutic strategies. By harnessing the power of rRNA regulation, we can unlock new insights into human health and disease, which will have important ramifications for early treatment and therapeutic development, particularly for CNS disorders where aberrant protein translation is considered key in disease development.

Looking forward, several open questions remain in the field of 2′-O-ribose methylation biology, especially regarding its role in neurological disorders. Key research directions include understanding the precise molecular mechanisms by which 2′-O-methylation influences neural function and identifying the specific rRNA residues whose modification or dysregulation is critical in the context of CNS disorders. Additionally, exploring how these modifications affect the broader landscape of synaptic plasticity and cognitive function could yield insights into the pathogenesis of neurodevelopmental and neurodegenerative diseases. Addressing these questions will be crucial in determining whether targeted manipulation of rRNA modifications could be a novel therapeutic approach for treating neurological conditions.

CRediT authorship contribution statement

Anuj K. Verma: Writing – original draft, Data curation. **Bhaskar Roy:** Writing – original draft, Data curation. **Yogesh Dwivedi:** Writing – review & editing, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

YD is supported by NIMH grants R01MH130539, R01MH124248, R01MH118884, R01MH128994, and R01MH107183). All figures were created with the BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39036.

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Glossary

snoRNP: A group of small nucleolar proteins localized to nucleolus to facilitate ribosome biogenesis and pre-rRNA processing and act like molecular chaperones.
Acrocentric chromosome: This is a type of chromosome where the centromere appears to be at one end of the chromosome structure.
snoRNA: A type of non-coding RNA widely present in the nucleoli and plays an important role in rRNA, tRNA, and mRNA modification.
Ribosomal protein: These proteins comprise structural parts of the ribosome and are essential for ribosomal assembly and function
RNA Polymerase I: This polymerase transcribes 47S pre-rRNA, an essential component of ribosome biogenesis.
Ribosomal heterogeneity: Ribosomal heterogeneity refers to differences in ribosome structure and function within a cell, which affect protein synthesis and cellular behavior.
Synaptic plasticity: This term refers to the activity-dependent modification of strength or efficacy of synaptic transmission in preexisting synapses.
Fibrillarin: It is a catalytic enzyme from the methyltransferase family that modifies the specific 2'-O-ribose sugar of the rRNA molecule following methylation.
Neural crest cells: Neural crest cells are multipotent migratory cells in vertebrate embryos that give rise to diverse cell types, including neurons, glia, and melanocytes.
Neural plates: The neural plate is a thickened layer of neuroectodermal cells on the dorsal side of the embryo with the ability to initiate neurulation.
Optic tectum: It is also called the superior colliculus, a midbrain structure critical in detecting and orienting to biologically significant events.
Yolk sac: It is an extra-embryonic membranous structure attached to the embryo and acting as a source of nutrients and protection with a future role in forming a circulatory system.
2'-O-Ribomethylation: 2'-O-Ribomethylation is the 2'-hydroxymethylation of the ribose sugar, predominantly occuring in rRNA molecules. Its functional role is to stabilize the RNA from enzymatic degradation and increase the RNA-protein interaction.