rRNA and tRNA Bridges to Neuronal Homeostasis in Health and Disease

Francesca Tuorto [1] **and Rosanna Parlato** [2,3]

1 - Division of Epigenetics, *DKFZ-ZMBH Alliance, German Cancer Research Center, Im Neuenheimer Feld 580, 69120 Heidelberg, Germany*
2 - Institute of Applied Physiology, *University of Ulm, Albert Einstein Allee 11, 89081 Ulm, Germany*
3 - Institute of Anatomy and Cell Biology, *Medical Cell Biology, University of Heidelberg, Im Neuenheimer Feld 307, 69120 Heidelberg, Germany*

Correspondence to Francesca Tuorto and Rosanna Parlato: *German Cancer Research Center, Im Neuenheimer Feld 580, 69120 Heidelberg, Germany. University of Ulm, Institute of Applied Physiology, Albert Einstein Allee, 11, 89081 Ulm, Germany. f.tuorto@dkfz.de, rosanna.parlato@uni-ulm.de*
https://doi.org/10.1016/j.jmb.2019.03.004
Edited by Ernst Stefan Seemann

Abstract

Dysregulation of protein translation is emerging as a unifying mechanism in the pathogenesis of many neuronal disorders. Ribosomal RNA (rRNA) and transfer RNA (tRNA) are structural molecules that have complementary and coordinated functions in protein synthesis. Defects in both rRNAs and tRNAs have been described in mammalian brain development, neurological syndromes, and neurodegeneration. In this review, we present the molecular mechanisms that link aberrant rRNA and tRNA transcription, processing and modifications to translation deficits, and neuropathogenesis. We also discuss the interdependence of rRNA and tRNA biosynthesis and how their metabolism brings together proteotoxic stress and impaired neuronal homeostasis.

Introduction

Types of RNA in a eukaryotic cell classically included ribosomal RNA (rRNA), transfer RNA (tRNA), and messenger RNA (mRNA). Over the last decade, advances in RNA-sequencing (RNA-seq) and transcriptome-wide analysis enabled the identification of an increasing variety of non-coding RNA, such as long non-coding RNA, microRNA, small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), piwiRNA, and circular RNA (circRNA) increasing the complexity of RNA-mediated regulation of physiological cellular processes and disease mechanisms [1]. Although rRNA and tRNA are usually excluded from these transcriptomic studies, recent findings promoted the need to revisit the function of these RNAs and their integration into mechanisms regulating protein synthesis and beyond. In addition, a novel class of small RNAs was revealed using the RNA-seq data [2,3]. For instance, the fragmentation of tRNAs gives rise to tRNA-derived small RNAs (tsRNAs) by the cleavage at specific positions [4]. There are two main types of tsRNAs: tRNA-derived fragments (tRFs; 14–30 nucleotides) and tiRNAs (tRNA-derived stress-induced RNAs, or tRNA halves, 28–36 nucleotides), both regulating the translation machinery and cellular homeostasis by multiple mechanisms, including mRNA stability, inhibition of translation initiation and elongation, and ribosome biogenesis [5–8].

Recent reviews have outlined the up-to-date functions of various RNA types in aging and age-related diseases [1,4,9]. Here, we emphasize the emerging roles of dysfunctional rRNA and tRNA in neurological disorders in particular, but not exclusively, those linked with cognitive decline and neurodegeneration. After a brief summary of the molecular and structural basis of rRNA and tRNA synthesis, we describe recent evidence of rRNA- and tRNA-mediated disease mechanisms. Finally, we discuss how this knowledge can help the identification of new therapeutic approaches and the development of disease markers.

Snapshots of rRNA Synthesis and Ribosome Biogenesis

rRNA synthesis takes place in the nucleolus, a nuclear compartment not surrounded by membrane in which ribosomal subunits are also assembled (Fig. 1). Each rDNA repeat unit consists of a conserved rRNA coding sequence transcribed by the RNA polymerase I (RNA Pol I) and non-conserved intergenic spacers. The mature 18S, 5.8S, and 28S rRNAs derive from an rRNA precursor transcript (47S pre-rRNA) separated by externally and internally transcribed spacers. The mature 80S ribosome is composed of two subunits: the small 40S ribosomal subunit that contains the 18S rRNA and 33 ribosomal proteins (RPs) and the large 60S ribosomal subunit that comprises the 28S, 5.8S, and 5S rRNAs and 47 RPs [10].

Notably, the nucleolus consists of three regions corresponding to three different steps in the synthesis of rRNA and characterized by the expression of typical markers with a specific role in rRNA synthesis. In particular, these regions are as follows: the fibrillar center (FC), where rDNA transcription takes place; the dense fibrillar component (DFC), where pre-rRNA is processed; and the granular component (GC), also containing processing factors and ribosomal proteins. At the electron microscopic level, FCs are fibrillar regions enriched with RNA Pol I–specific transcription factors including upstream binding transcription factor 1 (UBTF1). DFCs are highly electron-dense fibrillar regions that surround FCs. DFCs are labeled with antibodies specifically recognizing pre-rRNA processing factors including fibrillarin. GCs, the granular regions outside of FCs and DFCs, are enriched with assembly factors and ribosomal proteins. During processing, the pre-40S and the pre-60S ribosomal subunits are assembled and exported to the cytoplasm where the mature ribosomes are finally produced [11].

Ribosomal biogenesis is a process that requires the tight coordination of the transcriptional activity of all three RNA polymerases [12] that is in turn regulated by environmental changes. Post-translational modifications of protein components of the transcriptional machinery and histones as well as epigenetic modifications at the rDNA loci affect initiation of transcription [10]. Moreover, the structure and function of rRNAs are strongly influenced by a wide variety of post-transcriptional modifications. These modifications regulate rRNA folding and within the ribosome are located in regions interacting with tRNA and mRNA [9]. 2′-*O*-ribose-methylation (2′Ome) and pseudouridylation (Ψ) are the most frequent rRNA modifications in eukaryotes. Interestingly, these modifications are context-specific and depend on extracellular changes, developmental and disease state [13]. rRNA post-transcriptional modifications have various functions being located at functional sites within the ribosomes: they increase the stability of the ribosome, the precision of protein synthesis, and ribosomal specialization [14]. Importantly, not all ribosomes are structurally and functionally identical [13], and specialized ribosomes turn up to be a novel strategy to regulate gene expression [15]. The different affinity of ribosome components for specific mRNAs is an emerging mechanism by which translation controls gene expression [16]. It has been reported that subsets of mRNAs, involved in the response to oxidative stress, depend on the loss of specific rRNA modifications [17]. For example, the reduced expression of the RNA methyltransferase NSUN5, which catalyzes the post-transcriptional modification 5- methylcytidine (m^5C) in the 28S rRNA, results in both reduced rRNA methylation and altered translational fidelity, leading to increased stress resistance by the translation of proteins important for the stress response, for example, involved in DNA damage repair [17].

Interestingly, these rRNA modifications are regulated by nutrient availability and oxidative and heat shock stress, tightening ribosome biogenesis and function to environmental conditions, similarly to the reprogramming of tRNA modifications observed upon stress, that will be discussed later [18].

Moreover, the inhibition of rDNA transcription resulting in the loss of nucleolar integrity and release of nucleolar proteins in the nucleoplasm defines a condition known as “nucleolar stress” [19,20]. Lately, the functional implications of this condition have been expanded by new evidence of the highly dynamic nature of nucleolar assembly and associated changes in protein composition [21]. An imbalance in ribosome biogenesis, for example, by the accumulation of specific ribosomal proteins, may lead to an increased stability of the transcription factors p53, a major player in the response to different types of cellular stresses [22]. Interestingly, not only nucleolar proteins are important for rRNA synthesis, they may also regulate cell proliferation, differentiation, and cell death [23]. The association between the nucleolus and malignant cell transformation anticipated the hypothesis that this organelle might play an active role in disease pathogenesis rather than being an end-effect of neoplastic transformation [19,24–27]. In the last decade, a similar hypothesis peeked out in the context of neurodegenerative disorders [23,28–31]. Several mechanisms can be envisaged by which defective rRNA synthesis may have a deleterious impact on neuronal well-being, although surveillance mechanisms have been developed to detect and eliminate misprocessed rRNA. Intriguingly, a silencing mechanism that can inhibit pre-rRNA expression, if rRNA is not correctly processed, has been recently proposed [32].

As summarized in Fig. 1, rRNA synthesis could be dysregulated at different steps: changes in the number of rDNA genes, defective rDNA transcription, and

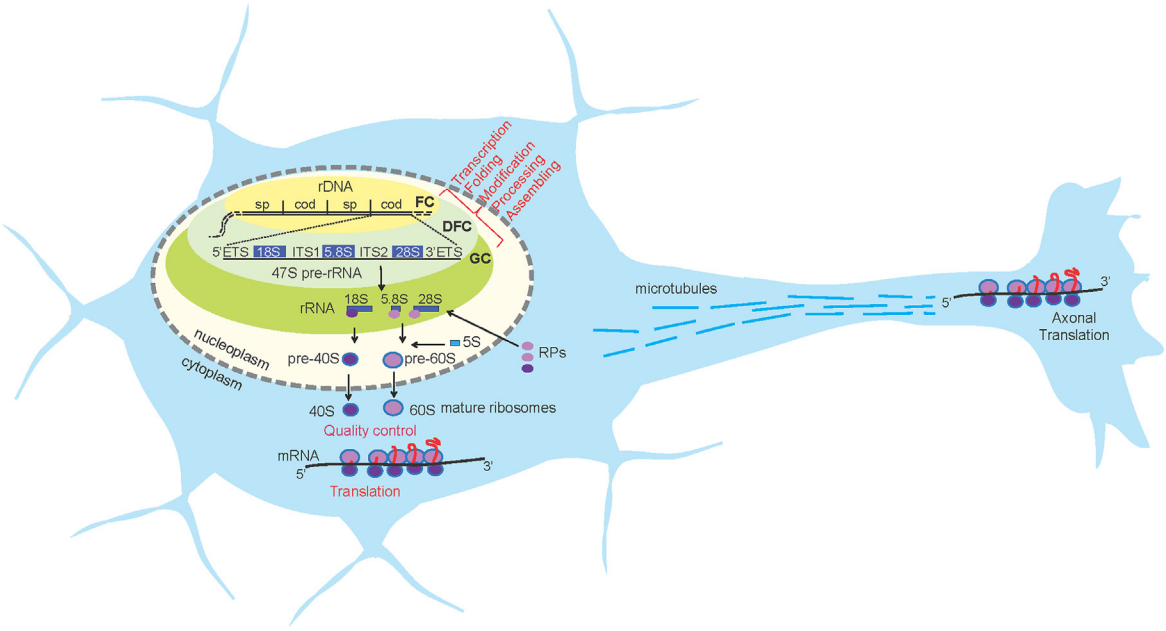

Fig. 1. Overview of the main steps of rRNA synthesis and ribosome biogenesis. Schematic representation showing rDNA genes, precursor-RNA transcription, and pre-ribosome assembly in the nucleolus (in the three sub-compartments: FC, FGC, and GC), while mature ribosome assembly and mRNA translation occur in the cytoplasm. Mature ribosomes as well as defective and misfolded proteins face quality control in the cytoplasm. The main critical steps that can be affected in a neurodegenerative context with toxic consequences on protein translation and neuronal function and survival are highlighted in red. Abbreviations: sp., spacer; cod, coding region; ETS, external transcribed spacer; ITS, internal transcribed spacer.

defective rRNA processing may result in defective ribosomes. The result could be the accumulation of aberrant proteins triggering the unfolded protein response and disrupting proteostasis. In any case, it is predictable that a deficit in protein synthesis, either in terms of overall decrease in translation or in terms of decreased accuracy leading to defective proteins, will have a major impact on neuronal processes underlying cognitive functions, even before the impact on neuronal survival. Because the role of dysfunctional ribosomes in neurodevelopmental disorders and pediatric neurodegeneration has been presented in-depth in a recent review, it will not be addressed here [33]. Examples of specific rRNA-mediated pathomechanisms in progressive neurodegenerative diseases are summarized in the section below.

Altered rRNA Synthesis in Neurodegenerative Diseases: Causes and Consequences

Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) are all neurodegenerative disorders characterized by the specific loss of particular populations of neurons and a complex spectrum of symptoms. HD is a genetic disorder of known origin; for all others, genetic causes have been also identified. Importantly, to explain variable disease onset and progression, environmental and genetic predisposition by modifier genes needs to be deeply understood. For all of these diseases, there is still no cure.

Here we present recent work showing that dysregulation in rRNA synthesis is a hallmark of these different neurodegenerative disorders, and that various mechanisms underlying a dysfunctional synthesis of rRNA exert toxicity and lead to neuronal death.

Synthesis of rRNA and AD

AD is a progressive age-related neurodegenerative disease characterized by the progressive loss of memory, executive function, language, and social behavior. One of the pathological features of AD is the oligomerization and aggregation of the amyloid β-peptide (Aβ), forming amyloid plaques in the brain, although their pathological role remains unclear [34].

Along with extracellular amyloid plaques, intracellular neurofibrillary tangles (NFTs) are hallmarks of AD in the brain. NFTs represent misfolded Tau (*t*ubulin-*a*ssociated *u*nit) aggregates resulting from the polymerization of modified Tau protein. Although the

mechanisms are still unclear, hyper-phosphorylated Tau confers neurotoxicity. Interestingly, Tau is a microtubule protein located in the nucleus and in the nucleolus as well as shown in undifferentiated and differentiated neuroblastoma (SHSY5Y) cells and in human brain tissue [35,36]. Recent evidence shows that Tau is involved under normal conditions in silencing rDNA, because upon knockdown of Tau, rDNA transcription increases in association with decreased heterochromatin and DNA methylation. Similarly, the re-localization of Tau under glutamate-induced cellular stress results in a decreased synthesis of the pre-rRNA and redistribution of nucleolar proteins such as fibrillarin (FBL) and UBTF1. Moreover, glutamate causes redistribution of nucleolar non-phosphorylated Tau leading to cell death [36]. Interestingly, the same group has shown that also Aβ42 oligomers by changing the distribution and phosphorylation status of Tau result in reduced rDNA transcription and levels of 18S and 28S rRNA in SHSY5Y cells [37]. The hypothesized cause is that Aβ42 oligomers increase oxidative stress and by changing tau phosphorylation and localization in the nucleolus impair rRNA synthesis at early stages, before neuronal death. Hence, these studies suggest perturbed nucleolar-dependent signaling as initial targets of toxic proteins in AD [37].

Interestingly, the genomic region containing the 18S rDNA increases in the parietal cortex of AD patients [38]. In the meantime, the increased copy number is associated with increased rDNA promoter methylation, a signature of epigenetic silencing of rDNA. Aged hippocampal neurons show down-regulation of rRNA transcription. Nevertheless, it remained unclear whether AD-associated epigenetic silencing is associated with neurodegeneration [38]. More recently, rDNA content and its methylation state have been investigated in the cerebral cortex and cerebellum of dementia-associated with Lewy bodies (DLB). rDNA instability has been found in brain-derived autopsies from patients with DLB in combination with rDNA expansion in the cerebral cortex, mostly affected by neurodegeneration in this disease [39]. It has been proposed that rDNA instability affects maintenance of heterochromatin with important implications for gene expression and global genome stability. This work supports a model in which lower rDNA content may enhance the DNA damage response, reducing control over euchromatic gene expression and destabilizing the chromatin architecture [39]. In turn, cells with the higher genomic content of rDNA may become overrepresented due to lower sensitivity to subsequent injuries. Thus, rDNA amplification in the degenerating regions of the DLB or AD brain may be a consequence of increased genotoxic stress [39]. These studies are particularly important in view of the high variability in the number of rDNA copies and the possibility of different levels of rRNA gene dosage that has been already described in other pathological contexts such as schizophrenia [40] and various cancers [41]. Interestingly, this variation in rDNA dosage in humans is inversely associated with mitochondrial DNA abundance, suggesting a link with mitochondrial function and oxidative damage as well [42]. This dosage-dependent regulation is even more complex given the discovery in mice of variant rRNA (v-RNA) alleles with tissue-specific expression that support the production of functionally specific ribosomes [43]. Initial evidence of differential expression of v-RNA in mice that underwent a hippocampus-dependent spatial memory task revealed an increased rRNA synthesis associated with the upregulation of a specific v-rRNA [44].

The role of the nucleolus and of rRNA transcription in spatial learning has been recently demonstrated by the effect of a compound CX-5461, a specific RNA Pol I inhibitor, resulting in impaired memory consolidation in mice [44–46]. Indeed, acute nucleolar disruption by treatment with CX-5461 prevented the maintenance of late-phase long-term potentiation (LTP) and memory consolidation [47].

Importantly, similar to dentate gyrus and hippocampus, the analysis of human cerebral cortex from middle-aged and AD stages I–VI revealed down-regulation of nucleolar proteins including nucleolin (NCL), nucleophosmin 1 (NPM1), and NPM3 and the UBTF1 at the mRNA and protein levels [48,49] along with several ribosomal proteins and component of the initiation and elongation translational machinery. Although there are stage- and region-specific differences, the most remarkable differences concern the comparison of these changes with those in the somatosensory cortex of APP/PS1 transgenic mice, used as a model of AD-like β-amyloidopathy: in this model, it seems that some of the rRNAs and NCL as well as RPs are upregulated [49], suggesting compensatory mechanisms, common to other mouse models, as explained in the case of PD genetic models in the next section.

In the context of early mechanisms associated with a dysfunctional nucleolus, we need to mention the possible role played by the chromatin-remodeling enzyme poly(ADP-ribose) polymerase-1 (PARP-1) important in synaptic plasticity and memory consolidation. Nucleolar PARP-1 in CA1 and CA4 hippocampal pyramidal cell neurons in AD is significantly reduced compared to controls [50]. The proposed model is that the absence of PARP-1 in nucleoli allows for methylation of rDNA promoters silencing rRNA transcription and resulting in nucleolar disruption [50].

Accordingly, we found that the induction of nucleolar stress based on the conditional genetic ablation of transcription initiation factor-IA (TIF-IA) in excitatory hippocampal neurons in mice resulted in decreased LTP [51]. However, it remains to be investigated the impact on protein synthesis, in particular whether the synthesis of specific proteins might be altered and whether “specialized” ribosomes play a role under

these circumstances. For example, initial evidence in the same model showed that despite inhibition of pre-rRNA synthesis, the total ribosome content was mildly reduced; nevertheless, the RNA Pol I activity was required for the pharmacological induction of seizures [52]. Interestingly, the expression of specific ribosomal proteins is upregulated by the induction of pharmacologic epilepsy, supporting the hypothesis of changes in ribosomal protein composition and in ribosomal translational function.

Synthesis of rRNA and PD

PD is the second most common neurodegenerative disease in patients older than 65 years. Over the past 10 years, considerable efforts have gone into improving diagnosis by imaging criteria and development of biomarkers [53].

Alterations of nucleolar volume have been reported already in 1982 in dopaminergic neurons of the vulnerable substantia nigra in PD and in cases of parkinsonism [54]. A later study, however, reported that nucleolar size was not correlated with the size of the typical presence of Lewy bodies [55].

We have shown that in PD human autopsies the level of rDNA transcription, as well as the distribution of nucleolar protein NPM1, is affected [56], and we also recently found that TIF-IA mRNA is reduced in PD dopaminergic neurons [57]. In essence, the nucleolus (function and/or integrity) is altered in both pharmacological PD models, based on neurotoxins such 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [56] and 6-hydroxydopamine (6-OHDA) [58,59]. Interestingly, also various genetic mutations known to be causative of PD affect rRNA synthesis in mouse models [57,60,61].

A systematic analysis of PD (Braak stages 1–6) and middle-aged (MA) brain tissues in various brain regions including substantia nigra showed that several components of the protein synthesis machinery from regulators of rRNA synthesis to factors regulating protein synthesis initiation are affected. In particular, reduced mRNA expression of several nucleolar proteins NCL, NPM1, NPM3, and UBTF1 and diminished 18S rRNA and 28S rRNA was found. Also the expression of several mRNAs encoding ribosomal protein subunits in the substantia nigra was reduced. Concomitantly, altered protein levels of initiation factor eIF3 and elongation factor eEF2 were found in the substantia nigra in PD. These observations further indicate marked region-dependent and stage-dependent alterations in the cerebral cortex in PD. Interestingly, the changes observed in substantia nigra and cerebral cortex are associated with the formation of α-synuclein oligomer promoting neurotoxicity [62,63]. In agreement with these findings, we found in a mouse model mildly overexpressing mutant human A53T α-synuclein that this protein localizes also at the nucleolus [57]. Interestingly, in this model, we observe an increased number of nucleoli labeled by various nucleolar markers at an early pre-symptomatic stage and a decreased rDNA transcription at later stages [57], suggesting early compensatory mechanisms.

In summary, these studies in human post-mortem tissue samples and in pharmacological and genetic PD models reveal that the integrity and function of the nucleolus are affected with different modalities during defined stages of the disease. The findings that the number of nucleoli is actually higher in association with a pre-symptomatic stage suggest that there might be metabolic compensatory mechanisms involving nucleolar signaling as well. The further characterization of this response requires additional studies, in particular the association between nucleolar dynamic and the accumulation of protein nuclear inclusions as well as the association with changes in other cellular organelles such the mitochondria.

In a mouse model of nucleolar stress in dopaminergic neurons induced by the conditional ablation of TIF-IA, we showed that this condition causes progressive neurodegeneration of substantia nigra dopaminergic neurons associated with parkinsonian-like phenotype, characterized by impaired motor coordination, downregulation of the mechanistic target of rapamycin (mTOR) pathway and induction of oxidative stress linked to reduced activity of the cytochrome *c* oxidase, reinforcing the hypothesis that nucleolar-dependent signaling events are relevant in PD progression [56,57].

Synthesis of rRNA in HD and ALS/FTD

Despite its known genetic origin caused by the expanded trinucleotide CAG repeat in the Huntingtin gene, our understanding of the complex pathomechanisms underlying this disease is still incomplete. The mutant Huntingtin (mHTT) protein affects several cellular functions hindering the identification of the primary pathogenic event [64,65].

Notably, Huntingtin and mHTT accumulate in the nucleus [47,66] and mHTT mRNA down-regulates rDNA transcription by interacting with NCL, while mHTT protein acts on the acetyltransferase CREB-binding protein (CBP), both required for the activity of the RNA Pol I and rDNA transcription [67–70]. Recently, the transcription factor peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) has been shown to localize to the nucleolus where it regulates the recruitment of RNA Pol I and UBTF1 to the rDNA promoter [71]. Interestingly, PGC-1α function is tightly linked to the cellular energetic status, showing a novel important factor regulating energy-dependent rDNA transcription. These observations are particularly interesting for their implications in HD pathomechanisms because PGC-1α is downregulated in HD patients [72]. Moreover, we have previously shown that rRNA synthesis is

impaired in the striatum of the rapid onset R6/2 transgenic mice overexpressing the N-terminus of the human mHTT at an early stage [73]. Despite these advances supporting the role of the nucleolus in HD, the interdependence between nucleolar dysfunction and the accumulation of mHTT nuclear inclusions in HD progression remained unexplored and it represents an important question for future research.

ALS and FTD are connected in a group of patients showing progressive degeneration of motor neurons and FTD. Problems in RNA homeostasis and protein translation are a major feature of these diseases, and excellent reviews have addressed their connection with neurodegeneration in ALS and FTD [74–77]. Moreover, we have recently reported the association and impact of the C9orf72 mutation in ALS/FTD with nucleolar dysfunction in a dedicated review [78]. Nevertheless, it is important to mention here even more recent studies, showing that neurotoxic poly-dipeptides that form aggregates in patients with the C9orf72 mutation, in particular poly-GR, are recruited by NPM1 into the nucleolus, resulting in reduced levels of ribosomes and translational rate in primary neurons [79]. However, in tissues from patients, these poly-peptides do not co-localize with the nucleolus [79,80], suggesting highly dynamic processes. Importantly, the analysis of mice expressing GFP-poly(GR)100 in the brain shows impaired protein translation and co-localize with ribosomal proteins, further supporting the role of protein synthesis dysregulation in this disease [81]. Although this study did not show decreased rRNA synthesis in degenerating neurons but rather a significant increase of pre-rRNA, it will be important to further understand its functional impact on neuronal homeostasis and disease progression [81].

In conclusion, the strong and early association between a dysfunctional nucleolus and age-related neurodegenerative disorders suggests an important role of nucleolar-dependent signaling in these diseases. In the next sections, we will show initial evidence of deficits of tRNA synthesis in various neurological disorders, although a link to neurodegenerative diseases, such as AD, PD, HD, and ALS/FTD, is still missing, and we will discuss the link between rRNA and tRNA deficits and convergence on dysfunctional ribosomes.

Snapshots of tRNA Synthesis and Maturation

tRNAs are central for the translation of the genetic code into polypeptides. In this process, they recognize the codons on the mRNA and carry the cognate amino acid to the nascent polypeptide. tRNAs have been among the earliest studied non-coding RNA molecules; indeed, the first to be characterized was an alanine tRNA from baker's yeast, and its structure was published already in 1965 [82]. However, tRNAs have received increasing attention in the recent years because of their role in translational control.

tRNAs are transcribed as a long precursor molecule that goes through several maturation steps before becoming functional for protein synthesis (Fig. 2a). Canonical tRNA genes contain highly conserved motive residues located at predictable distances one from each other. The secondary structure resembles a "cloverleaf model" with stems and loops (Fig. 2b). The single chain of tRNA is folded on itself to form five arms. As a result of this folding, the 3′-end and 5′-end lie adjacent to each other. Each arm consists of a basal stalk and a loop. Two of the arms have a loop, a D-loop that contains the modified nucleotide dihydrouridine and a Tψc-loop that contains thymine, a base usually found in DNA and ψ, with a ribosome recognition site. The third arm known as "variable arm" has a stem with optional loop. At one end of the chains, with a double-stranded structure in which the 5′ and 3′ ends are adjacent to each other, the amino acid acceptor stem attaches to the amino acid by the activity of specific aminoacyl-tRNA synthetase. Mature tRNAs display a three-dimensional L-structure through intermolecular hydrogen bonding to position the amino acid binding site at one end and the anticodon at the other end. The anticodon is a three-nucleotide sequence that interacts with an mRNA codon through complementary base pairing. During the translation process, charged tRNAs are properly and dynamically positioned within the ribosome. This process is mediated by specific interactions not only with mRNA but also with translation factors and ribosomal components [83].

In the human genome, 417 tRNA genes are predicted for 47 anticodons of largely unequal copy number (http://gtrnadb.ucsc.edu/genomes/eukaryota/Hsapi19/) that decode the 20 standard amino acids, plus selenocysteine [84]. tRNA genes with the same anticodon sequences and different body are termed "isodecoders," while "isoacceptors" are tRNA genes that read synonymous mRNA codons, which are different codons for the same amino acid. The expression of isodecoders is tissue-specific [85] and can be differentially altered under diseases such as cancer [86,87].

tRNAs in eukaryotes are transcribed by RNA Pol III and tRNA gene annotation and tRNA quantification has been obtained by RNA polymerase III chromatin immunoprecipitation sequencing (ChIP-seq) [88] on the assumption that RNA Pol III binding always leads to a productive and completely processed tRNA molecule. However, as for the pre-rRNA, to become functional, tRNAs undergo a series of processing steps and chemical modifications including the following: trimming of 5′ leader and 3′ trailer, splicing of introns, modifications of nucleosides, and addition of CCA [89]. The 5′ processing of precursor tRNA occurs by cleavage by RNase P, usually before 3′ processing that is a more complex process. A major

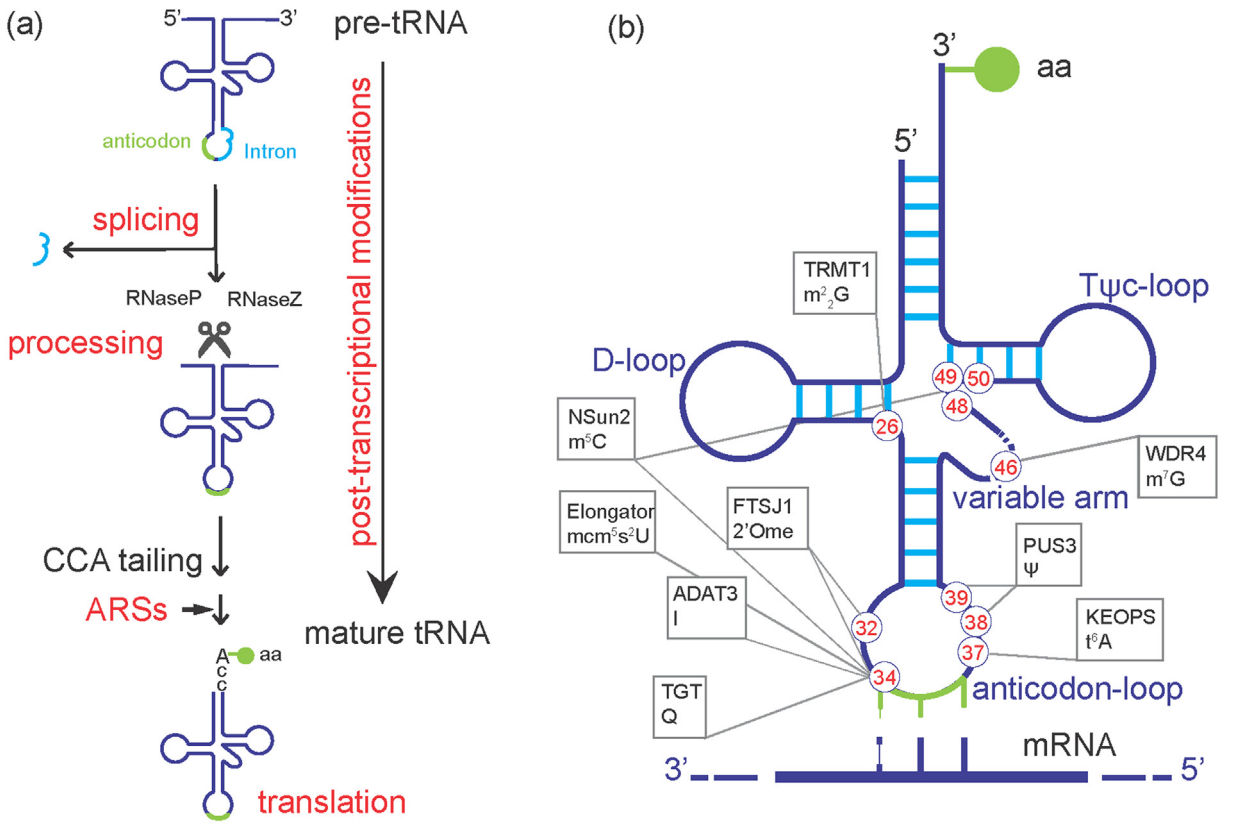

Fig. 2. Synthesis and structure of tRNA including post-transcriptional modifications. (a) The main steps of tRNA synthesis are summarized here, as described in the text. The processes affected in various neurological disorders are highlighted in red. (b) Cloverleaf model with stems and loop showing the secondary structure of mature tRNA. Modifications and enzymes underlying deficits of tRNA and consequently of translational functions are highlighted, including those known to be involved in various neurological disorders (see text for details).

pathway for 3′ processing is catalyzed by the RNase Z, which cut the 3′ trailer to generate a new 3′ end site to which CCA is added. Precursor RNA 3′ end formation begins with RNA Pol III termination generating a variable length 3′ UUU_N motive recognized by La binding chaperones. These are a conserved class of eukaryotic RNA-binding proteins that assist folding and processing of tRNAs and other transcripts synthesized by the RNA polymerase III [90]. La binding protects RNA 3′ end from exonucleolytic digestion that would otherwise be degraded by the nuclear surveillance system and facilitates the RNAseZ endonucleolytic removal of the pre-tRNA trailer [91]. Alternatively, RNA Pol III-intrinsic 3′ exoribonuclease activity mediated by the subunit Rpc11p can digest the trailer until the discriminator base and the CCA can then be added [91]. Interestingly, La function is regulated by stress. Indeed, upon DNA damage, nuclear localization of phosphorylated La is altered, and La is dephosphorylated and removed from the nuclear pre-tRNAs [92].

Notably, tRNA gene transcription occurs in the nucleolus; indeed, tRNA genes, though dispersed in the genome, co-localize with 5S ribosomal DNA and U14 snRNA at the nucleolus [93]. Before exiting the nucleus, pre-tRNAs undergo processing at their 5′ and 3′ ends as well as numerous nucleoside modifications. tRNAs are delivered to the cytoplasm in a step termed “primary tRNA nuclear export.” While alternative export mechanisms exist, export of tRNA by exportin-t, for example, requires fully processed tRNA, providing a mean to proofread tRNAs before they leave the nucleus [94]. Surprisingly, tRNA nuclear-cytoplasmic traffic is bidirectional. Cytoplasmic tRNAs are imported back to the nucleus by the “tRNA retrograde nuclear import” step and again back to cytoplasm via “tRNA nuclear re-export”. At each of these steps, tRNAs undergo maturation processes, chemical modifications, and eventually repair [94]. This traffic has been hijacked by viruses, such as HIV, that seems to use tRNAs to promote the nuclear import of the reverse transcription complex [95].

This dynamic relocalization between the nucleus, cytoplasm, and also mitochondrial surface is conserved from budding yeast to vertebrate cells, and tRNA nuclear accumulation is observed in budding yeast under nutrient deprivation [96]. Contextually, it

has been observed that initiator $tRNA^{Met}$ is actively translocated into the nucleus of human cells under heat stress [97].

The spatial re-distribution of the translation machinery is a process of particular importance in neurons, in particular for synaptic local translation, and it is tempting to speculate that mechanisms that modulate neuronal protein translation may act by sequestration of cytoplasmic tRNAs in the nucleus or other compartments away from the protein synthesis machinery.

Altered tRNA Synthesis and Modifications in Neurological Disorders

As for the rRNA, disruption of any tRNA maturation steps can impair the production of mature molecules, altering the cellular tRNA pool and impacting neuronal homeostasis on multiple levels. For example, mutations in the largest catalytic core of Pol III as well as in the various cytoplasmic aminoacyl-tRNA synthetases that catalyze the aminoacylation of specific amino acids in the tRNA have been linked to Hypomyelinating Leukodystrophies. These represent genetic neurodegenerative disorders characterized by insufficient myelin deposition during development with a clinical manifestation that often includes early-onset nystagmus, ataxia, and spasticity. The hypothesized pathogenetic mechanisms involve impaired availability of tRNAs resulting in reduced translation capacity and insufficient myelin deposition [98].

Moreover, a broad range of central and peripheral nervous system diseases is caused by pathogenic variants in genes encoding aminoacyl-tRNA synthetases and their interacting proteins, for example, the Charcot–Marie–Tooth disease type 2D or epileptic encephalopathy [98]. However, the bases of the specific effects on myelination are still not understood. The specific expression of isodecoder represents an additional potential mechanism. For example, in mutant mice, a genomic mutation that significantly reduces the expression of a $tRNA^{Arg}_{UCU}$ isodecoder specifically expressed in the brain increased ribosome pausing at AGA codons and resulted in neurodegeneration, likely due to protein misfolding [99], explaining the cell-specific phenotype.

An additional process that when dysfunctional may underlie tRNA-deficit-dependent neurodegeneration is tRNA splicing. Twenty-eight human tRNA genes contain introns that need to be removed to produce mature tRNAs by the tRNA splicing endonuclease complex (TSEN) [100,101]. Interestingly, brain transcripts show the highest level of alternative splicing compared to those transcribed in other tissues, and it has been proposed that mutations in components of the splicing machinery can account for specific neurological disorders [102]. In addition, new evidence suggests that in the mammalian cortex, the RNA-binding protein La could also interact with nuclear pre-tRNA splicing intermediates and it could regulate the tRNA maturation pathway [90,103]. A molecular link between tRNA splicing and neurodegeneration is demonstrated by mutations in the TSEN complex. Indeed, mutations in several family components (TSEN2, TSEN15, TSEN34, and TSEN54) have been identified in pontocerebellar hypoplasias, a heterogeneous group of neurodegenerative disorders with prenatal to neonatal onset characterized by cerebellar hypoplasia and microcephaly [100,104]. Notably, a putative non-catalytic mutation in TSEN54 that is highly expressed in the pons and cerebellar dentate regions of the developing brain suggests the cause of these tissue-specific deficits [104]. Another molecular link between tRNA splicing and pontocerebellar hypoplasia is demonstrated by mutations in the cleavage and polyadenylation factor 1 (CLIP1), which abrogate the interaction of pre-tRNA with TSEN complex. This causes a reduction in pre-tRNA cleavage and an accumulation of non-spliced tRNA and fragments [105,106].

It remains unclear whether changes in the levels of mature tRNAs and accompanying defects in translation elongation are involved in the disease mechanism. Alternatively, the accumulation of aberrant intermediate tRNA fragments derived from the aberrant processing of intron-containing tRNAs may impact disease pathology [105,106].

All RNA species carry modified nucleosides, and RNA modifications are particularly enriched in cytoplasmic and mitochondrial tRNAs, with over 80 modifications reported [107]. This process represents another important possibility of defective tRNA function and translational dysregulation. Indeed a human tRNA can contain between 11 and 13 different modifications that are deposited at different steps during its maturation and that regulate the structure and function of tRNAs, influencing all aspects of tRNA activity including decoding [108–110]. The modification range from simple methylation like 2′Ome, 1-methyladenosine (m^1A), and m^5C can be the result of base isomerization reactions like Ψ, but some RNA nucleotides also carry rather complex modifications such as queuosine (Q). A big variety of modifications are located in the tRNA anticodon loop, where they play a key role in the codon/anticodon pairing, reading frame maintenance, and decoding process. In particular, position 34, corresponding to the first base of the anticodon loop of tRNAs, is subject to various modifications, depending on the tRNA isoacceptor [110].

The human brain is particularly sensitive to tRNA modifications defects, and several neurological disorders have be attributed to mutations in genes that affect the tRNA post-transcriptional modifications [111]. Besides their direct role in RNA stability, folding, and binding, these modifications may act as

sensors that transduce altered metabolic state, due to stress inputs, to translational output [112]. In the following section, we will discuss distinct tRNA modifications that have been primarily connected to neurological disorders.

tRNA modifications associated with neurological disorders

Mature tRNAs are heavily modified post-transcriptionally, and these modifications are essential for tRNA structure, stability, and function. The function of a modification depends on both its location in the tRNA structure and its chemical nature. As reported below, several human diseases, including neurological disorders, have been linked to mutations in enzymes that modify the tRNA [111].

Inosine (I) at the tRNA position 34 is produced by adenosine deamination catalyzed by the *het*erodimeric *a*denosine *d*eaminase enzymes *a*cting on *t*RNAs (hetADAT). Inosine in the tRNA anticodon expands the decoding capacity of individual tRNAs, therefore reducing the required number of tRNA species for codon–anticodon recognition [113]. A missense mutation in adenosine deaminase tRNA specific 3 (ADAT3), one subunit of hetADAT, leads to intellectual disability (ID) and strabismus, indicating the functional relevance of the I34 editing for proper neuronal development [114].

5-Methylcytidine (m^5C) stabilizes the tRNA structure and protects tRNAs against endonucleolytic cleavage by the ribonuclease 5 (also known as angiogenin, or ANG) [115,116]. C48, C49, and C50 of the vast majority of tRNAs, as well as C34 in the anticodon loop of $tRNA^{Leu}_{CCU}$, are methylated by the methyltransferase NSun2 [116,117], C72 in $tRNA^{Cys}$ and $tRNA^{Thr}$ by NSun6 [118], and C38 of $tRNA^{Asp,Gly,Val}$ by Dnmt2 [116]. Loss of DNMT2-mediated methylation at the anticodon loop causes both tRNA-specific fragmentation and codon-specific mistranslation. The double knockout of Dnmt2 and NSun2 in mice revealed the importance of m^5C for global protein translation and cortex differentiation [116]. In addition, human and mouse genetics variants of *NSUN2* have also been linked to microcephaly, cortical atrophy, and ID such as is seen in Dubowitz-like syndrome [119–121]. In both human and mouse model systems, the loss of m^5C methylation leads to an accumulation of tRNA fragments. Furthermore, treatment of Nsun2-deficient mice with the ANG inhibitor N65828 inhibited cleavage of tRNA, reduced stress granule formation, and rescued apoptosis in response to cellular stress, suggesting that accumulation of cleaved 5′ tRNA fragments may play a role in the pathogenesis and that ANG inhibition may represent a potential treatment [119].

ID is a highly heterogeneous disorder defined by limitations both in intellectual functioning and in adaptive behavior expressed by conceptual, social, and practical adaptive skills. ID seems a common feature of several autosomal mutations identified in tRNA modification genes. Indeed in addition to the above-described ADAT3 and NSUN2 mutations, a homozygous truncation mutation in PUS3 was recently shown to segregate with ID. PUS3 is a member of the highly conserved TruA/Pus3 family of pseudouridylases, which catalyzes isomerization of uridine to Ψ at U38 and 39 in the anticodon-stem loop of tRNAs [122]. Another example is the tRNA methyltransferase 1 (TRMT1) that catalyze the formation of dimethylation of guanosines ($m^2{}_2G$) at position 26 of several tRNAs. Inactivation of this gene by a homozygous frameshift mutation is a biomarker for recessive ID and cognitive disorders [123].

Another strong link between ID and a tRNA modification gene is shown in non-syndromic X-linked ID (NSXLID) due to mutations in FTSJ1, a methyltransferase that catalyzes the 2′-*O*-ribose methylation of nucleotides at positions 32 and 34 of the substrate tRNAs [124].

A prominent role assigned to Elongator, a multisubunit protein complex of 6 ELP proteins, is the modification of wobbles uridine, U34 in cytoplasmic tRNAs. Elongator is required for the addition of 5-methoxycarbonylmethyl (mcm^5), 5-carbamoylmethyl (ncm^5), or 5-methoxycarbonylmethyl-2-thiouridine (mcm^5s^2U) groups to U34 of 11 tRNA species in yeast, and this function is conserved in nematodes and mammals [125]. Elongator subunits ELP2 have also been linked to ID [126], whereas other Elongator subunits have been associated with a wide range of neurological disorders. Human variants of *ELP3* have been associated with ALS, familial dysautonomia (FD), and motor neuron degeneration [123,127]. Depletion of the Elongator complex component Elp3 in mutant mice triggers the unfolded protein response (UPR) through interference with codon translation speed. UPR activation impairs the balance between direct and indirect neurogenesis, leading to premature differentiation [128]. Also *ELP1* mutations have been linked to autosomal recessive FD, a hereditary sensory and autonomic neuropathy characterized by the progressive degeneration of the sensory and autonomic nervous system. FD patients showed a mutation in the donor splice site of intron 20 of the *ELP1* gene, resulting in aberrant splicing [129], and their cerebrum and fibroblasts have reduced levels of mcm^5s^2 modifications at tRNA U34 [130]. Finally, mutations of *ELP4* have been reported also in a benign form of child epilepsy affecting motor function, atypical rolandic epilepsy, in which Elongator depletion resulted in the brain-specific down-regulation of genes implicated in cell motility and migration [131].

In addition to the pathologies connected with cognitive disorders, there is a growing list of human neurological diseases linked to abnormal tRNA modification associated with severe growth

phenotypes, for example, a form of severe microcephalic primordial dwarfism with brain malformation (microcephaly, agenesis of corpus callosum, and simplified gyration), a severe encephalopathy with seizure, and global developmental delay caused by mutation of WDR4, a subunit of the methyltransferase that catalyzes 7-methylguanosine modification of residue G46 of tRNA [132]. Recently, homozygous mutations in the kinase-associated endopeptidase KAE1, which functions in the biosynthesis of *N*6-threonylcarbamoyladenosine (t^6A) modifications at nucleotide 37 in the anticodon stem loop of nearly all tRNAs decoding ANN (where N is any nucleotide) codons, have been linked to a severe microcephaly. The patients showed failure to thrive, with microcephaly, nystagmus, hypotonia, and gross motor delay, with both comprehensive and expressive language skills being severely impaired [133].

Queuosine (Q) is a 7-deaza-guanosine nucleoside that is irreversibly incorporated by a base-exchange reaction at position G34 into tRNAs with GUN anticodons by the tRNA-guanine transglycosylase (TGTase) enzymatic complex. Eukaryotes obtain the queuine base or its analogs, as a micronutrient from dietary sources and from the gut microbiota [134,135]. We recently demonstrated that nutrition-dependent levels of queuosinylated tRNA (Q-tRNA) control protein translation on the translatome scale. Indeed, reduced Q-tRNA and the consequent reduced $m^5C38\text{-}tRNA^{Asp}_{GUC}$ modification affect translational speed at cognate codons [136]. Their cumulative effects deregulate protein translation by modifying the amino acid composition of the cellular proteome, resulting in unfolded proteins, protein aggregates, endoplasmic reticulum stress, and altered cell growth signaling. Germ-free mouse model (axenic mice) fed a Q-free synthetic diet-depleted Q-tRNA from highly proliferative tissues, such as the liver, whereas the brain retained high levels of Q-tRNA, an efficient salvage mechanism of this metabolite in neurons [136]. Deficiency of queuine in human HepG2 cells and mouse mutants for the TGTase complex shows impaired ability to produce tyrosine from phenylalanine [137] with the potential to influence production of monoamine neurotransmitters such as dopamine, with potential implications for neurological disorders related to dopamine imbalance that, however, remain to be investigated. Furthermore, in a mouse model of multiple sclerosis, recent evidence suggests that queuine tRNA incorporation contributes to the pervasive encephalomyelitis observed in this disease [138]. The administration of a *de novo* designed eukaryotic TGTase substrate (NPPDAG) relieved clinical symptoms in mouse models due to reduction in effector immune cell proliferation and activation [138].

All described links between tRNA modifications enzymes and the consequent abnormal brain development and neurological disorders point to a functional association between aberrant tRNA modifications and development of neurological disease, presumably because of impaired protein synthesis, due to a direct effect of modifications on decoding properties, due to fidelity and translation elongation, or because lack of some modifications affects tRNA stability, tRNA fragments accumulation, and by that the protein synthesis machinery.

rRNA and tRNA Synthesis: Converging Neuropathogenic Mechanisms

As indicated above, rRNA and tRNA synthesis and functions are strongly linked to the stress conditions [139]. At the structural level, rRNA and tRNA interact within the ribosomes in multiple points to ensure a correct positioning and function. Hence, the production of aberrant rRNA and tRNA due, for example, to defects in their synthesis, processing, and post-transcriptional modifications (Figs. 1 and 2) may have deleterious consequences on protein synthesis [9]. Both tRNA and rRNA share similar if not identical chemical modifications that are responsible for folding, stability, and translation performances. tRNA selection inside ribosomes may affect decoding properties of elongating ribosomes, in response to genetic instances, environmental cues, and stress conditions. Although this convergence between rRNA and tRNA is predictable, some examples clearly show potential mechanisms underlying their relationship in a neuropathological context.

On this side, mutations in the ribonuclease ANG, which mediates the cleavage of tRNAs, have been linked to familial and sporadic ALS and PD [140,141]. In particular, most missense mutations in ANG that inhibit its RNAase activity are associated with ALS [142]. Moreover, variants in the ANG gene are also associated with PD [143] and AD [144].

ANG is a neuroprotective factor that prevents neuronal death induced by various stresses [145]. Stress conditions may induce the re-localization of various ribonucleases from the nucleus to the cytoplasm, including ANG that promotes formation of blood vessels and the survival of motor neurons [146]. Under stress conditions, ANG is accumulated in cytoplasmic compartments and modulates the production of tiRNA, which have been implicated in inhibition of protein synthesis, formation of stress granules, inhibition of apoptosis via interaction with cyt *c*, and alteration in tiRNAs biogenesis, which have been linked to broad ranges of human disease syndromes [147]. Thus, ANG-mediated tiRNAs reprogram protein translation, save anabolic energy, and promote cell survival [148]. Otherwise, under growth stimuli, ANG translocates to the nucleus, where it stimulates rRNA transcription accumulating in the nucleolus, thus promoting cell

growth [149]. Therefore, ANG can both stimulate rRNA transcription and degrade tRNA [140,150]. This dual function connects reduced rRNA transcription and degradation of tRNA, a mechanism of protein synthesis reprogramming during stress [151,152].

Intriguingly, Q modification protects cognate full-length tRNAs against ANG and alters the cellular content of their fragments *in vivo* depending on cellular stress [153], similarly to the protection observed by Dnmt2-mediated methylation [115]. Furthermore, Dnmt2-dependent tRNA methylation is dynamically modulated by queuosine [136]. These characteristics link diet and microbiome that strongly influence queuosine to the regulation of protein synthesis in the cellular stress response.

Recently, it has been shown that a specific tRNA fragment, $tsRNA^{Leu}_{CAG}$, decreased the abundance of 40S and 80S ribosomal complexes and increased 60S, suggesting impaired assembly of the 80S ribosome. This led to the discovery that $tsRNA^{Leu}_{CAG}$ acts at the translational level on the biosynthesis of specific ribosomal proteins, RPS28 and RPS15, while their mRNA abundance was not affected. These data support the hypothesis that $tsRNA^{Leu}_{CAG}$ is involved in unfolding the duplexed secondary structures of RP mRNAs at the mRNA targeting site, thus facilitating ribosome protein biogenesis [154]. Another example of convergence between rRNA and tRNA is the observation that the conditional knockout of La, the RNA binding protein that protects nascent RNA synthesized by RNA Pol III from 3′ exonucleases, results in progressive neurodegeneration. Interestingly, non-phosphorylated La is located in the nucleolus in the DFC and interacts with NCL, involved in rRNA biogenesis [155]. Phosphorylated La instead is located in the nucleoplasm, where it associates with the nascent pre-tRNAs. The La knockout mice show increased 5.8S rRNA and defective pre-tRNA and pre-rRNA processing leading to progressive neurodegeneration with loss of cortical brain mass [155].

Other neurological disorders are associated with both mutations in the RNA Pol I and decreased RNA Pol III activity such as hypomyelinating leukodystrophies and with deficits of tRNA splicing and rRNA processing due to mutations of the exosome component 3 (EXOSC3) in pontocerebellar hypoplasia [106,156].

These studies represent initial examples of mechanisms connecting rRNA and tRNA synthesis and processing that are of potential pathogenic relevance, and although at this point one can only speculate about their role, this research direction promises important progresses for our understanding of protein and neuronal homeostasis.

Concluding Remarks and Perspectives

One of the hallmarks of neurodegenerative diseases is the accumulation of protein inclusions and translational deficits might account for altered protein homeostasis with a toxic impact on cell functions and survival.

As presented here, deficits in rRNA and tRNA synthesis and processing have strong effects on neuronal function and survival, and multiple modalities account for their toxic impact. An imbalance in any of their biosynthetic steps may result in dysfunctional protein synthesis altering cellular homeostasis. It is somehow predictable that deficits in rRNA and tRNA functions have severe consequences for the cells. Current evidence suggests that rRNA and tRNA dysfunctions might affect the neurodegenerative process, for example, by highly specific and selective functions within the protein synthesis. It remains unclear whether deficits in either rRNA or tRNA biosynthesis have a causative role in neurodegenerative diseases and/or modify disease progression. Although these are fundamental questions and further research is needed in this direction, it is equally important to understand to which extent neurons are sensitive to such imbalance and what are the compensatory mechanisms adopted to cope with a deficit in transcription and/or processing and maturation of rRNA and/or tRNA.

Both rRNA and tRNA syntheses are strongly regulated by cellular stress signals and environmental changes and could be secondary consequences of the degenerative process. It is tempting to speculate that the specific impact of the gut microbiome and nutrient availability on rRNA and tRNA synthesis might help to better understand the influence of nutrition on the neurodegenerative process. For example, diminished tryptophan-dependent protein biosynthesis has been reported in AD patients and tryptophanyl-tRNA synthetase (TrpRS) deficiency results in hippocampal neurodegeneration in mice [157,158].

Effective treatments halting disease progression will depend on targeting the pathological mechanisms before the onset of the symptoms. A large effort in the search for effective therapies is directed toward the identification of genetic causes to “fix the problem at the origin.” Nevertheless, it seems also evident that these are multifactorial diseases and a combination of strategies to alter the course of the disease represents a valid parallel research direction. To this end, it will be crucial to investigate in greater detail at what stages rRNA and tRNA are dysfunctional, whether these are associated with altered synthesis of specific proteins and might be due to aberrant or insufficient number of individual tRNAs or ribosomes and/or lack of specialized ribosomes, or due to defective neuronal proteostasis as a consequence of altered translational speed and accuracy.

In perspective, a deeper understanding of rRNA and tRNA context-specific functions but also of their molecular interdependence might help to identify targeted therapeutic strategies and the potential side effects of therapeutic metabolic intervention.

Acknowledgment

This work was supported by grants from the Deutsche Forschungsgemeinschaft (DFG): DFG TU5371-1 to F.T. and DFG PA 1529/2-1 to R.P. FT was supported by the DKFZ NCT3.0 Integrative Project in Cancer Research (NCT3.0_2015.54 DysregPT) and the Institute of Genetics and Biophysics "A. Buzzati-Traverso, C.N.R.," Naples (Italy).

Received 10 December 2018;
Received in revised form 25 February 2019;
Accepted 6 March 2019
Available online 12 March 2019

Keywords:
rRNA;
tRNA;
protein synthesis;
neurological disorders;
cellular stress

Abbreviations used:
2′Ome, 2′-*O*-ribose-methylation; 6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; ADAT3, adenosine deaminase tRNA specific 3; ALS, amyotrophic lateral sclerosis; ANG, angiogenin; Aβ, amyloid β-peptide; CBP, acetyltransferase CREB-binding protein; ChIP-seq, chromatin immunoprecipitation sequencing; circRNA, circular RNA; CLIP1, cleavage and polyadenylation factor 1; DFC, dense fibrillar component; DLB, dementia-associated with Lewy bodies; eEF2, elongation factor2; eIF3, initiation factor3; ETS, external transcribed spacer; FBL, fibrillarin; FC, fibrillar center; FD, familial dysautonomia; FTD, frontotemporal dementia; GC, granular component; HD, Huntington's disease; hetADAT, *het*erodimeric *a*denosine *d*eaminase; I, inosine; ID, intellectual disability; ITS, internal transcribed spacer; KAE1, kinase-associated endopeptidase; LTP, long-term potentiation; m^1A, 1-methyladenosine; $m^2{}_2G$, dimethyl oguanosine; m^5C, 5-methylcytidine; mcm^5, 5-methoxycarbonylmethyl; mcm^5s^2U, 5-methoxycarbonylmethyl-2-thiouridine; mHTT, mutant Huntingtin; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mRNA, messenger RNA; NCL, nucleolin; ncm^5, 5-carbamoylmethyl; NFTs, neurofibrillary tangles; NPM1, nucleopshosmin 1; NPM3, nucleopshosmin 3; PARP-1, poly(ADP-ribose) polymerase-1; PD, Parkinson's disease; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; Q-tRNA, queuosinylated tRNA; Q, queuosine; RNA Pol I, RNA polymerase I; RNA-seq, RNA-sequencing; RP, ribosomal proteins; rRNA, ribosomal RNA; snoRNA, small nucleolar RNA; snRNA, small nuclear RNA; t^6A, *N*6-threonylcarbamoyladenosine; tau, tubulin-associated unit; TGTase, tRNA-guanine transglycosylase; TIF-IA, transcription initiation factor-IA; tiRNAs, tRNA-derived stress induced fragments; tRFs, tRNA-derived fragments; TRMT1, tRNA methyltransferase 1; tRNA, transfer RNA; TSEN, tRNA splicing endonuclease complex; tsRNAs, tRNA-derived small RNAs; UBTF1, upstream binding transcription factor 1; UPR, unfolded protein response; v-RNA, rRNA variant; Ψ, pseudouracil.

References

[1] J.C. Gomez-Verjan, E.R. Vazquez-Martinez, N.A. Rivero-Segura, R.H. Medina-Campos, The RNA world of human ageing, Hum. Genet. 137 (2018) 865–879.
[2] Y.S. Lee, Y. Shibata, A. Malhotra, A. Dutta, A novel class of small RNAs: tRNA-derived RNA fragments (tRFs), Genes Dev. 23 (2009) 2639–2649.
[3] A.E. Cozen, E. Quartley, A.D. Holmes, E. Hrabeta-Robinson, E.M. Phizicky, T.M. Lowe, ARM-seq: AlkB-facilitated RNA methylation sequencing reveals a complex landscape of modified tRNA fragments, Nat. Methods 12 (2015) 879–884.
[4] Y. Shen, X. Yu, L. Zhu, T. Li, Z. Yan, J. Guo, Transfer RNA-derived fragments and tRNA halves: biogenesis, biological functions and their roles in diseases, J. Mol. Med. (Berl.) 96 (2018) 1167–1176.
[5] P. Anderson, P. Ivanov, tRNA fragments in human health and disease, FEBS Lett. 588 (2014) 4297–4304.
[6] J. Shi, Y. Zhang, T. Zhou, Q. Chen, tsRNAs: the Swiss army knife for translational regulation, Trends Biochem. Sci. 44 (2019) 185–189.
[7] V. Oberbauer, M.R. Schaefer, tRNA-derived small RNAs: biogenesis, modification, function and potential impact on human disease development, Genes (Basel) 9 (2018).
[8] S. Li, Z. Xu, J. Sheng, tRNA-derived small RNA: a novel regulatory small non-coding RNA, Genes (Basel) 9 (2018).
[9] A. Bastide, A. David, Interaction of rRNA with mRNA and tRNA in translating mammalian ribosome: functional implications in health and disease, Biomolecules 8 (2018).
[10] S. Sharifi, H. Bierhoff, Regulation of RNA polymerase I transcription in development, disease, and aging, Annu. Rev. Biochem. 87 (2018) 51–73.
[11] A. Nemeth, I. Grummt, Dynamic regulation of nucleolar architecture, Curr. Opin. Cell Biol. 52 (2018) 105–111.
[12] L. Nunez Villacis, M.S. Wong, L.L. Ferguson, N. Hein, A.J. George, K.M. Hannan, New roles for the nucleolus in health and disease, Bioessays 40 (2018), e1700233.
[13] K.E. Sloan, A.S. Warda, S. Sharma, K.D. Entian, D.L.J. Lafontaine, M.T. Bohnsack, Tuning the ribosome: the influence of rRNA modification on eukaryotic ribosome biogenesis and function, RNA Biol. 14 (2017) 1138–1152.
[14] S. Sharma, V. Marchand, Y. Motorin, D.L.J. Lafontaine, Identification of sites of 2′-*O*-methylation vulnerability in human ribosomal RNAs by systematic mapping, Sci. Rep. 7 (2017) 11490.
[15] M. Buszczak, R.A. Signer, S.J. Morrison, Cellular differences in protein synthesis regulate tissue homeostasis, Cell 159 (2014) 242–251.
[16] S. Xue, M. Barna, Specialized ribosomes: a new frontier in gene regulation and organismal biology, Nat. Rev. Mol. Cell Biol. 13 (2012) 355–369.
[17] M. Schosserer, N. Minois, T.B. Angerer, M. Amring, H. Dellago, E. Harreither, A. Calle-Perez, A. Pircher, M.P. Gerstl, S. Pfeifenberger, C. Brandl, M. Sonntagbauer, A. Kriegner, A. Linder, A. Weinhausel, T. Mohr, M. Steiger, D. Mattanovich, M. Rinnerthaler, T. Karl, S. Sharma, K.D. Entian, M. Kos, M. Breitenbach, I.B. Wilson, N. Polacek, R. Grillari-Voglauer, L. Breitenbach-Koller, J. Grillari, Methylation of ribosomal RNA

by NSUN5 is a conserved mechanism modulating organismal lifespan, Nat. Commun. 6 (2015) 6158.
[18] H.Y. Huang, A.K. Hopper, Multiple layers of stress-induced regulation in tRNA biology, Life (Basel) 6 (2016).
[19] C.P. Rubbi, J. Milner, Disruption of the nucleolus mediates stabilization of p53 in response to DNA damage and other stresses, EMBO J. 22 (2003) 6068–6077.
[20] S. Boulon, Y. Ahmad, L. Trinkle-Mulcahy, C. Verheggen, A. Cobley, P. Gregor, E. Bertrand, M. Whitehorn, A.I. Lamond, Establishment of a protein frequency library and its application in the reliable identification of specific protein interaction partners, Mol. Cell. Proteomics 9 (2010) 861–879.
[21] M. Feric, N. Vaidya, T.S. Harmon, D.M. Mitrea, L. Zhu, T.M. Richardson, R.W. Kriwacki, R.V. Pappu, C.P. Brangwynne, Coexisting liquid phases underlie nucleolar subcompartments, Cell 165 (2016) 1686–1697.
[22] M.O. Olson, Sensing cellular stress: another new function for the nucleolus? Sci. STKE 2004 (2004), pe10.
[23] M. Hetman, M. Pietrzak, Emerging roles of the neuronal nucleolus, Trends Neurosci. 35 (2012) 305–314.
[24] J.E. Quin, J.R. Devlin, D. Cameron, K.M. Hannan, R.B. Pearson, R.D. Hannan, Targeting the nucleolus for cancer intervention, Biochim. Biophys. Acta 1842 (2014) 802–816.
[25] L. Montanaro, D. Trere, M. Derenzini, Nucleolus, ribosomes, and cancer, Am. J. Pathol. 173 (2008) 301–310.
[26] M. Derenzini, D. Trere, A. Pession, M. Govoni, V. Sirri, P. Chieco, Nucleolar size indicates the rapidity of cell proliferation in cancer tissues, J. Pathol. 191 (2000) 181–186.
[27] M.O. Olson, M. Dundr, A. Szebeni, The nucleolus: an old factory with unexpected capabilities, Trends Cell Biol. 10 (2000) 189–196.
[28] K. Kalita, D. Makonchuk, C. Gomes, J.J. Zheng, M. Hetman, Inhibition of nucleolar transcription as a trigger for neuronal apoptosis, J. Neurochem. 105 (2008) 2286–2299.
[29] R. Parlato, G. Kreiner, G. Erdmann, C. Rieker, S. Stotz, E. Savenkova, S. Berger, I. Grummt, G. Schutz, Activation of an endogenous suicide response after perturbation of rRNA synthesis leads to neurodegeneration in mice, J. Neurosci. 28 (2008) 12759–12764.
[30] R. Parlato, G. Kreiner, Nucleolar activity in neurodegenerative diseases: a missing piece of the puzzle? J. Mol. Med. (Berl.) 91 (2013) 541–547.
[31] Y. Shin, C.P. Brangwynne, Liquid phase condensation in cell physiology and disease, Science 357 (2017).
[32] C. Zhu, Q. Yan, C. Weng, X. Hou, H. Mao, D. Liu, X. Feng, S. Guang, Erroneous ribosomal RNAs promote the generation of antisense ribosomal siRNA, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) 10082–10087.
[33] M. Hetman, L.P. Slomnicki, Ribosomal biogenesis as an emerging target of neurodevelopmental pathologies, J. Neurochem. 148 (2019) 325–347.
[34] D.J. Selkoe, Alzheimer's disease, Cold Spring Harb. Perspect. Biol. 3 (2011).
[35] M. Bukar Maina, Y.K. Al-Hilaly, L.C. Serpell, Nuclear Tau and its potential role in Alzheimer's disease, Biomolecules 6 (2016) 9.
[36] M.B. Maina, L.J. Bailey, S. Wagih, L. Biasetti, S.J. Pollack, J.P. Quinn, J.R. Thorpe, A.J. Doherty, L.C. Serpell, The involvement of tau in nucleolar transcription and the stress response, Acta Neuropathol. Commun. 6 (2018) 70.
[37] M.B. Maina, L.J. Bailey, A.J. Doherty, L.C. Serpell, The involvement of Abeta42 and Tau in nucleolar and protein synthesis machinery dysfunction, Front. Cell. Neurosci. 12 (2018) 220.
[38] M. Pietrzak, G. Rempala, P.T. Nelson, J.J. Zheng, M. Hetman, Epigenetic silencing of nucleolar rRNA genes in Alzheimer's disease, PLoS One 6 (2011), e22585.
[39] J. Hallgren, M. Pietrzak, G. Rempala, P.T. Nelson, M. Hetman, Neurodegeneration-associated instability of ribosomal DNA, Biochim. Biophys. Acta 1842 (2014) 860–868.
[40] L.N. Porokhovnik, N.A. Lyapunova, Dosage effects of human ribosomal genes (rDNA) in health and disease, Chromosom. Res. 27 (2019) 5–17.
[41] S.A. Ament, J.R. Pearl, A. Grindeland, J. St Claire, J.C. Earls, M. Kovalenko, T. Gillis, J. Mysore, J.F. Gusella, J.M. Lee, S. Kwak, D. Howland, M.Y. Lee, D. Baxter, K. Scherler, K. Wang, D. Geman, J.B. Carroll, M.E. MacDonald, G. Carlson, V.C. Wheeler, N.D. Price, L.E. Hood, High resolution time-course mapping of early transcriptomic, molecular and cellular phenotypes in Huntington's disease CAG knock-in mice across multiple genetic backgrounds, Hum. Mol. Genet. 26 (2017) 913–922.
[42] J.G. Gibbons, A.T. Branco, S. Yu, B. Lemos, Ribosomal DNA copy number is coupled with gene expression variation and mitochondrial abundance in humans, Nat. Commun. 5 (2014) 4850.
[43] M.M. Parks, C.M. Kurylo, R.A. Dass, L. Bojmar, D. Lyden, C.T. Vincent, S.C. Blanchard, Variant ribosomal RNA alleles are conserved and exhibit tissue-specific expression, Sci. Adv. 4 (2018), eaao0665.
[44] K.D. Allen, M.J. Regier, C. Hsieh, P. Tsokas, M. Barnard, S. Phatarpekar, J. Wolk, T.C. Sacktor, A.A. Fenton, A.I. Hernandez, Learning-induced ribosomal RNA is required for memory consolidation in mice—evidence of differentially expressed rRNA variants in learning and memory, PLoS One 13 (2018), e0203374.
[45] J.H. Stehle, O. Rawashdeh, Ribosomal RNA—a tail wagging the dog? J. Neurochem. 136 (2016) 673–676.
[46] F. Capitano, C. Gargiuli, A. Angerilli, K. Maccaroni, F. Pelliccia, A. Mele, G. Camilloni, RNA polymerase I transcription is modulated by spatial learning in different brain regions, J. Neurochem. 136 (2016) 706–716.
[47] K.D. Allen, A.V. Gourov, C. Harte, P. Gao, C. Lee, D. Sylvain, J.M. Splett, W.C. Oxberry, P.S. van de Nes, M.J. Troy-Regier, J. Wolk, J.M. Alarcon, A.I. Hernandez, Nucleolar integrity is required for the maintenance of long-term synaptic plasticity, PLoS One 9 (2014), e104364.
[48] K. Hernandez-Ortega, P. Garcia-Esparcia, L. Gil, J.J. Lucas, I. Ferrer, Altered machinery of protein synthesis in Alzheimer's: from the nucleolus to the ribosome, Brain Pathol. 26 (2016) 593–605.
[49] P. Garcia-Esparcia, G. Sideris-Lampretsas, K. Hernandez-Ortega, O. Grau-Rivera, T. Sklaviadis, E. Gelpi, I. Ferrer, Altered mechanisms of protein synthesis in frontal cortex in Alzheimer disease and a mouse model, Am. J. Neurodegener. Dis. 6 (2017) 15–25.
[50] J. Zeng, J. Libien, F. Shaik, J. Wolk, A.I. Hernandez, Nucleolar PARP-1 expression is decreased in Alzheimer's disease: consequences for epigenetic regulation of rDNA and cognition, Neural Plast. 2016 (2016) 8987928.
[51] A. Kiryk, K. Sowodniok, G. Kreiner, J. Rodriguez-Parkitna, A. Sonmez, T. Gorkiewicz, H. Bierhoff, M. Wawrzyniak, A.K. Janusz, B. Liss, W. Konopka, G. Schutz, L. Kaczmarek, R. Parlato, Impaired rRNA synthesis triggers homeostatic responses in hippocampal neurons, Front. Cell. Neurosci. 7 (2013) 207.
[52] A. Vashishta, L.P. Slomnicki, M. Pietrzak, S.C. Smith, M. Kolikonda, S.P. Naik, R. Parlato, M. Hetman, RNA polymerase

1 is transiently regulated by seizures and plays a role in a pharmacological kindling model of epilepsy, Mol. Neurobiol. 55 (2018) 8374–8387.
[53] Z. Walker, K.L. Possin, B.F. Boeve, D. Aarsland, Lewy body dementias, Lancet 386 (2015) 1683–1697.
[54] D.M. Mann, P.O. Yates, Pathogenesis of Parkinson's disease, Arch. Neurol. 39 (1982) 545–549.
[55] H.J. Gertz, A. Siegers, J. Kuchinke, Stability of cell size and nucleolar size in Lewy body containing neurons of substantia nigra in Parkinson's disease, Brain Res. 637 (1994) 339–341.
[56] C. Rieker, D. Engblom, G. Kreiner, A. Domanskyi, A. Schober, S. Stotz, M. Neumann, X. Yuan, I. Grummt, G. Schutz, R. Parlato, Nucleolar disruption in dopaminergic neurons leads to oxidative damage and parkinsonism through repression of mammalian target of rapamycin signaling, J. Neurosci. 31 (2011) 453–460.
[57] V. Evsyukov, A. Domanskyi, H. Bierhoff, S. Gispert, R. Mustafa, F. Schlaudraff, B. Liss, R. Parlato, Genetic mutations linked to Parkinson's disease differentially control nucleolar activity in pre-symptomatic mouse models, Dis. Model. Mech. 10 (2017) 633–643.
[58] M. Healy-Stoffel, S.O. Ahmad, J.A. Stanford, B. Levant, Altered nucleolar morphology in substantia nigra dopamine neurons following 6-hydroxydopamine lesion in rats, Neurosci. Lett. 546 (2013) 26–30.
[59] M. Healy-Stoffel, S. Omar Ahmad, J.A. Stanford, B. Levant, Differential effects of intrastriatal 6-hydroxydopamine on cell number and morphology in midbrain dopaminergic subregions of the rat, Brain Res. 1574 (2014) 113–119.
[60] H. Kang, J.H. Shin, Repression of rRNA transcription by PARIS contributes to Parkinson's disease, Neurobiol. Dis. 73 (2015) 220–228.
[61] S. Vilotti, M. Codrich, M. Dal Ferro, M. Pinto, I. Ferrer, L. Collavin, S. Gustincich, S. Zucchelli, Parkinson's disease DJ-1 L166P alters rRNA biogenesis by exclusion of TTRAP from the nucleolus and sequestration into cytoplasmic aggregates via TRAF6, PLoS One 7 (2012), e35051.
[62] P. Garcia-Esparcia, K. Hernandez-Ortega, A. Koneti, L. Gil, R. Delgado-Morales, E. Castano, M. Carmona, I. Ferrer, Altered machinery of protein synthesis is region- and stage-dependent and is associated with alpha-synuclein oligomers in Parkinson's disease, Acta Neuropathol. Commun. 3 (2015) 76.
[63] M.L. Choi, S. Gandhi, Crucial role of protein oligomerization in the pathogenesis of Alzheimer's and Parkinson's diseases, FEBS J. 285 (2018) 3631–3644.
[64] S. Kloppel, S. Gregory, E. Scheller, L. Minkova, A. Razi, A. Durr, R.A. Roos, B.R. Leavitt, M. Papoutsi, G.B. Landwehrmeyer, R. Reilmann, B. Borowsky, H. Johnson, J.A. Mills, G. Owen, J. Stout, R.I. Scahill, J.D. Long, G. Rees, S.J. Tabrizi, Track-On i, Compensation in preclinical Huntington's disease: evidence from the track-on HD study, EBioMedicine 2 (2015) 1420–1429.
[65] Genetic Modifiers of Huntington's Disease C, Identification of genetic factors that modify clinical onset of Huntington's disease, Cell 162 (2015) 516–526.
[66] P. Hilditch-Maguire, F. Trettel, L.A. Passani, A. Auerbach, F. Persichetti, M.E. MacDonald, Huntingtin: an iron-regulated protein essential for normal nuclear and perinuclear organelles, Hum. Mol. Genet. 9 (2000) 2789–2797.
[67] J. Lee, Y.J. Hwang, J.H. Boo, D. Han, O.K. Kwon, K. Todorova, N.W. Kowall, Y. Kim, H. Ryu, Dysregulation of upstream binding factor-1 acetylation at K352 is linked to impaired ribosomal DNA transcription in Huntington's disease, Cell Death Differ. 18 (2011) 1726–1735.
[68] J. Lee, Y.J. Hwang, H. Ryu, N.W. Kowall, H. Ryu, Nucleolar dysfunction in Huntington's disease, Biochim. Biophys. Acta 1842 (2014) 785–790.
[69] H. Tsoi, T.C. Lau, S.Y. Tsang, K.F. Lau, H.Y. Chan, CAG expansion induces nucleolar stress in polyglutamine diseases, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 13428–13433.
[70] H. Tsoi, H.Y. Chan, Expression of expanded CAG transcripts triggers nucleolar stress in Huntington's disease, Cerebellum 12 (2013) 310–312.
[71] S. Jesse, H. Bayer, M.C. Alupei, M. Zugel, M. Mulaw, F. Tuorto, S. Malmsheimer, K. Singh, J. Steinacker, U. Schumann, A.C. Ludolph, K. Scharffetter-Kochanek, A. Witting, P. Weydt, S. Iben, Ribosomal transcription is regulated by PGC-1alpha and disturbed in Huntington's disease, Sci. Rep. 7 (2017) 8513.
[72] L. Cui, H. Jeong, F. Borovecki, C.N. Parkhurst, N. Tanese, D. Krainc, Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration, Cell 127 (2006) 59–69.
[73] G. Kreiner, H. Bierhoff, M. Armentano, J. Rodriguez-Parkitna, K. Sowodniok, J.R. Naranjo, L. Bonfanti, B. Liss, G. Schutz, I. Grummt, R. Parlato, A neuroprotective phase precedes striatal degeneration upon nucleolar stress, Cell Death Differ. 20 (2013) 1455–1464.
[74] E.M. Lehmkuhl, D.C. Zarnescu, Lost in translation: evidence for protein synthesis deficits in ALS/FTD and related neurodegenerative diseases, Adv. Neurobiol. 20 (2018) 283–301.
[75] D. Ito, M. Hatano, N. Suzuki, RNA binding proteins and the pathological cascade in ALS/FTD neurodegeneration, Sci. Transl. Med. 9 (2017).
[76] T. Arzberger, M.H. Schludi, C. Lehmer, B. Schmid, D. Edbauer, RNA versus protein toxicity in C9orf72 ALS/FTLD, Acta Neuropathol. 135 (2018) 475–479.
[77] E.M. Tank, C. Figueroa-Romero, L.M. Hinder, K. Bedi, H.C. Archbold, X. Li, K. Weskamp, N. Safren, X. Paez-Colasante, C. Pacut, S. Thumma, M.T. Paulsen, K. Guo, J. Hur, M. Ljungman, E.L. Feldman, S.J. Barmada, Abnormal RNA stability in amyotrophic lateral sclerosis, Nat. Commun. 9 (2018) 2845.
[78] D. Herrmann, R. Parlato, C9orf72-associated neurodegeneration in ALS–FTD: breaking new ground in ribosomal RNA and nucleolar dysfunction, Cell Tissue Res. 373 (2018) 351–360.
[79] H. Hartmann, D. Hornburg, M. Czuppa, J. Bader, M. Michaelsen, D. Farny, T. Arzberger, M. Mann, F. Meissner, D. Edbauer, Proteomics and C9orf72 neuropathology identify ribosomes as poly-GR/PR interactors driving toxicity, Life Sci. Alliance 1 (2018), e201800070.
[80] M.H. Schludi, S. May, F.A. Grasser, K. Rentzsch, E. Kremmer, C. Kupper, T. Klopstock, German Consortium for Frontotemporal Lobar D, Bavarian Brain Banking A, T. Arzberger, D. Edbauer, Distribution of dipeptide repeat proteins in cellular models and C9orf72 mutation cases suggests link to transcriptional silencing, Acta Neuropathol. 130 (2015) 537–555.
[81] Y.J. Zhang, T.F. Gendron, M.T.W. Ebbert, A.D. O'Raw, M. Yue, K. Jansen-West, X. Zhang, M. Prudencio, J. Chew, C.N. Cook, L.M. Daughrity, J. Tong, Y. Song, S.R. Pickles, M. Castanedes-Casey, A. Kurti, R. Rademakers, B. Oskarsson, D.W. Dickson, W. Hu, A.D. Gitler, J.D. Fryer, L. Petrucelli, Poly(GR) impairs protein translation and stress granule dynamics in C9orf72-associated frontotemporal dementia and amyotrophic lateral sclerosis, Nat. Med. 24 (2018) 1136–1142.

[82] R.W. Holley, J. Apgar, G.A. Everett, J.T. Madison, M. Marquisee, S.H. Merrill, J.R. Penswick, A. Zamir, Structure of a ribonucleic acid, Science 147 (1965) 1462–1465.
[83] I.B. Lomakin, T.A. Steitz, The initiation of mammalian protein synthesis and mRNA scanning mechanism, Nature 500 (2013) 307–311.
[84] P.P. Chan, T.M. Lowe, GtRNAdb 2.0: an expanded database of transfer RNA genes identified in complete and draft genomes, Nucleic Acids Res. 44 (2016) D184–D189.
[85] B.M. Schmitt, K.L. Rudolph, P. Karagianni, N.A. Fonseca, R.J. White, I. Talianidis, D.T. Odom, J.C. Marioni, C. Kutter, High-resolution mapping of transcriptional dynamics across tissue development reveals a stable mRNA-tRNA interface, Genome Res. 24 (2014) 1797–1807.
[86] H. Gingold, D. Tehler, N.R. Christoffersen, M.M. Nielsen, F. Asmar, S.M. Kooistra, N.S. Christophersen, L.L. Christensen, M. Borre, K.D. Sorensen, L.D. Andersen, C.L. Andersen, E. Hulleman, T. Wurdinger, E. Ralfkiaer, K. Helin, K. Gronbaek, T. Orntoft, S.M. Waszak, O. Dahan, J.S. Pedersen, A.H. Lund, Y. Pilpel, A dual program for translation regulation in cellular proliferation and differentiation, Cell 158 (2014) 1281–1292.
[87] H. Goodarzi, H.C.B. Nguyen, S. Zhang, B.D. Dill, H. Molina, S.F. Tavazoie, Modulated expression of specific tRNAs drives gene expression and cancer progression, Cell 165 (2016) 1416–1427.
[88] A.J. Oler, R.K. Alla, D.N. Roberts, A. Wong, P.C. Hollenhorst, K.J. Chandler, P.A. Cassiday, C.A. Nelson, C.H. Hagedorn, B.J. Graves, B.R. Cairns, Human RNA polymerase III transcriptomes and relationships to Pol II promoter chromatin and enhancer-binding factors, Nat. Struct. Mol. Biol. 17 (2010) 620–628.
[89] E.M. Phizicky, A.K. Hopper, tRNA biology charges to the front, Genes Dev. 24 (2010) 1832–1860.
[90] N.H. Blewett, R.J. Maraia, La involvement in tRNA and other RNA processing events including differences among yeast and other eukaryotes, Biochim. Biophys. Acta Gene Regul. Mech. 1861 (2018) 361–372.
[91] R.J. Maraia, T.N. Lamichhane, 3′ Processing of eukaryotic precursor tRNAs, Wiley Interdiscip. Rev. RNA 2 (2011) 362–375.
[92] R.V. Intine, S.A. Tenenbaum, A.L. Sakulich, J.D. Keene, R. J. Maraia, Differential phosphorylation and subcellular localization of La RNPs associated with precursor tRNAs and translation-related mRNAs, Mol. Cell 12 (2003) 1301–1307.
[93] M. Thompson, R.A. Haeusler, P.D. Good, D.R. Engelke, Nucleolar clustering of dispersed tRNA genes, Science 302 (2003) 1399–1401.
[94] K. Chatterjee, R.T. Nostramo, Y. Wan, A.K. Hopper, tRNA dynamics between the nucleus, cytoplasm and mitochondrial surface: location, location, location, Biochim. Biophys. Acta Gene Regul. Mech. 1861 (2018) 373–386.
[95] L. Zaitseva, R. Myers, A. Fassati, tRNAs promote nuclear import of HIV-1 intracellular reverse transcription complexes, PLoS Biol. 4 (2006), e332.
[96] H.Y. Huang, A.K. Hopper, Separate responses of karyopherins to glucose and amino acid availability regulate nucleocytoplasmic transport, Mol. Biol. Cell 25 (2014) 2840–2852.
[97] R. Miyagawa, R. Mizuno, K. Watanabe, K. Ijiri, Formation of tRNA granules in the nucleus of heat-induced human cells, Biochem. Biophys. Res. Commun. 418 (2012) 149–155.
[98] M.I. Mendes, M. Gutierrez Salazar, K. Guerrero, I. Thiffault, G.S. Salomons, L. Gauquelin, L.T. Tran, D. Forget, M.S. Gauthier, Q. Waisfisz, D.E.C. Smith, C. Simons, M.S. van der Knaap, I. Marquardt, A. Lemes, H. Mierzewska, B. Weschke, W. Koehler, B. Coulombe, N.I. Wolf, G. Bernard, Bi-allelic mutations in EPRS, encoding the glutamyl-prolyl-aminoacyl-tRNA synthetase, cause a hypomyelinating leukodystrophy, Am. J. Hum. Genet. 102 (2018) 676–684.
[99] R. Ishimura, G. Nagy, I. Dotu, H. Zhou, X.L. Yang, P. Schimmel, S. Senju, Y. Nishimura, J.H. Chuang, S.L. Ackerman, RNA function. Ribosome stalling induced by mutation of a CNS-specific tRNA causes neurodegeneration, Science 345 (2014) 455–459.
[100] M.W. Breuss, T. Sultan, K.N. James, R.O. Rosti, E. Scott, D. Musaev, B. Furia, A. Reis, H. Sticht, M. Al-Owain, F.S. Alkuraya, M.S. Reuter, R. Abou Jamra, C.R. Trotta, J.G. Gleeson, Autosomal-recessive mutations in the tRNA splicing endonuclease subunit TSEN15 cause pontocerebellar hypoplasia and progressive microcephaly, Am. J. Hum. Genet. 99 (2016) 228–235.
[101] T. Yoshihisa, Handling tRNA introns, archaeal way and eukaryotic way, Front. Genet. 5 (2014) 213.
[102] G. Yeo, D. Holste, G. Kreiman, C.B. Burge, Variation in alternative splicing across human tissues, Genome Biol. 5 (2004) R74.
[103] S. Gaidamakov, O.A. Maximova, H. Chon, N.H. Blewett, H. Wang, A.K. Crawford, A. Day, N. Tulchin, R.J. Crouch, H.C. Morse III, R.D. Blitzer, R.J. Maraia, Targeted deletion of the gene encoding the La autoantigen (Sjogren's syndrome antigen B) in B cells or the frontal brain causes extensive tissue loss, Mol. Cell. Biol. 34 (2014) 123–131.
[104] B.S. Budde, Y. Namavar, P.G. Barth, B.T. Poll-The, G. Nurnberg, C. Becker, F. van Ruissen, M.A. Weterman, K. Fluiter, E.T. te Beek, E. Aronica, M.S. van der Knaap, W. Hohne, M.R. Toliat, Y.J. Crow, M. Steinling, T. Voit, F. Roelenso, W. Brussel, K. Brockmann, M. Kyllerman, E. Boltshauser, G. Hammersen, M. Willemsen, L. Basel-Vanagaite, I. Krageloh-Mann, L.S. de Vries, L. Sztriha, F. Muntoni, C.D. Ferrie, R. Battini, R.C. Hennekam, E. Grillo, F.A. Beemer, L.M. Stoets, B. Wollnik, P. Nurnberg, F. Baas, tRNA splicing endonuclease mutations cause pontocerebellar hypoplasia, Nat. Genet. 40 (2008) 1113–1118.
[105] A.E. Schaffer, V.R. Eggens, A.O. Caglayan, M.S. Reuter, E. Scott, N.G. Coufal, J.L. Silhavy, Y. Xue, H. Kayserili, K. Yasuno, R.O. Rosti, M. Abdellateef, C. Caglar, P.R. Kasher, J.L. Cazemier, M.A. Weterman, V. Cantagrel, N. Cai, C. Zweier, U. Altunoglu, N.B. Satkin, F. Aktar, B. Tuysuz, C. Yalcinkaya, H. Caksen, K. Bilguvar, X.D. Fu, C.R. Trotta, S. Gabriel, A. Reis, M. Gunel, F. Baas, J.G. Gleeson, CLP1 founder mutation links tRNA splicing and maturation to cerebellar development and neurodegeneration, Cell 157 (2014) 651–663.
[106] E. Karaca, S. Weitzer, D. Pehlivan, H. Shiraishi, T. Gogakos, T. Hanada, S.N. Jhangiani, W. Wiszniewski, M. Withers, I.M. Campbell, S. Erdin, S. Isikay, L.M. Franco, C. Gonzaga-Jauregui, T. Gambin, V. Gelowani, J.V. Hunter, G. Yesil, E. Koparir, S. Yilmaz, M. Brown, D. Briskin, M. Hafner, P. Morozov, T.A. Farazi, C. Bernreuther, M. Glatzel, S. Trattnig, J. Friske, C. Kronnerwetter, M.N. Bainbridge, A. Gezdirici, M. Seven, D.M. Muzny, E. Boerwinkle, M. Ozen, Baylor Hopkins Center for Mendelian G, T. Clausen, T. Tuschl, A. Yuksel, A. Hess, R.A. Gibbs, J. Martinez, J.M. Penninger, J.R. Lupski, Human CLP1 mutations alter tRNA biogenesis, affecting both peripheral and central nervous system function, Cell 157 (2014) 636–650.

[107] P. Boccaletto, M.A. Machnicka, E. Purta, P. Piatkowski, B. Baginski, T.K. Wirecki, V. de Crecy-Lagard, R. Ross, P.A. Limbach, A. Kotter, M. Helm, J.M. Bujnicki, MODOMICS: a database of RNA modification pathways. 2017 update, Nucleic Acids Res. 46 (2018) D303–D307.
[108] S. Kirchner, Z. Ignatova, Emerging roles of tRNA in adaptive translation, signalling dynamics and disease, Nat. Rev. Genet. 16 (2015) 98–112.
[109] Z. Durdevic, M. Schaefer, tRNA modifications: necessary for correct tRNA-derived fragments during the recovery from stress? Bioessays 35 (2013) 323–327.
[110] F. Tuorto, F. Lyko, Genome recoding by tRNA modifications, Open Biol. 6 (2016).
[111] A. Bednarova, M. Hanna, I. Durham, T. VanCleave, A. England, A. Chaudhuri, N. Krishnan, Lost in translation: defects in transfer RNA modifications and neurological disorders, Front. Mol. Neurosci. 10 (2017) 135.
[112] M. Helm, J.D. Alfonzo, Posttranscriptional RNA modifications: playing metabolic games in a cell's chemical Legoland, Chem. Biol. 21 (2014) 174–185.
[113] E.M. Novoa, M. Pavon-Eternod, T. Pan, L. Ribas de Pouplana, A role for tRNA modifications in genome structure and codon usage, Cell 149 (2012) 202–213.
[114] A.M. Alazami, H. Hijazi, M.S. Al-Dosari, R. Shaheen, A. Hashem, M.A. Aldahmesh, J.Y. Mohamed, A. Kentab, M.A. Salih, A. Awaji, T.A. Masoodi, F.S. Alkuraya, Mutation in ADAT3, encoding adenosine deaminase acting on transfer RNA, causes intellectual disability and strabismus, J. Med. Genet. 50 (2013) 425–430.
[115] M. Schaefer, T. Pollex, K. Hanna, F. Tuorto, M. Meusburger, M. Helm, F. Lyko, RNA methylation by Dnmt2 protects transfer RNAs against stress-induced cleavage, Genes Dev. 24 (2010) 1590–1595.
[116] F. Tuorto, R. Liebers, T. Musch, M. Schaefer, S. Hofmann, S. Kellner, M. Frye, M. Helm, G. Stoecklin, F. Lyko, RNA cytosine methylation by Dnmt2 and NSun2 promotes tRNA stability and protein synthesis, Nat. Struct. Mol. Biol. 19 (2012) 900–905.
[117] S. Blanco, A. Kurowski, J. Nichols, F.M. Watt, S.A. Benitah, M. Frye, The RNA-methyltransferase Misu (NSun2) poises epidermal stem cells to differentiate, PLoS Genet. 7 (2011), e1002403.
[118] S. Haag, A.S. Warda, J. Kretschmer, M.A. Gunnigmann, C. Hobartner, M.T. Bohnsack, NSUN6 is a human RNA methyltransferase that catalyzes formation of m5C72 in specific tRNAs, RNA 21 (2015) 1532–1543.
[119] S. Blanco, S. Dietmann, J.V. Flores, S. Hussain, C. Kutter, P. Humphreys, M. Lukk, P. Lombard, L. Treps, M. Popis, S. Kellner, S.M. Holter, L. Garrett, W. Wurst, L. Becker, T. Klopstock, H. Fuchs, V. Gailus-Durner, M. Hrabe de Angelis, R.T. Karadottir, M. Helm, J. Ule, J.G. Gleeson, D.T. Odom, M. Frye, Aberrant methylation of tRNAs links cellular stress to neuro-developmental disorders, EMBO J. 33 (2014) 2020–2039.
[120] L. Abbasi-Moheb, S. Mertel, M. Gonsior, L. Nouri-Vahid, K. Kahrizi, S. Cirak, D. Wieczorek, M.M. Motazacker, S. Esmaeeli-Nieh, K. Cremer, R. Weissmann, A. Tzschach, M. Garshasbi, S.S. Abedini, H. Najmabadi, H.H. Ropers, S.J. Sigrist, A.W. Kuss, Mutations in NSUN2 cause autosomal-recessive intellectual disability, Am. J. Hum. Genet. 90 (2012) 847–855.
[121] F.J. Martinez, J.H. Lee, J.E. Lee, S. Blanco, E. Nickerson, S. Gabriel, M. Frye, L. Al-Gazali, J.G. Gleeson, Whole exome sequencing identifies a splicing mutation in NSUN2 as a cause of a Dubowitz-like syndrome, J. Med. Genet. 49 (2012) 380–385.
[122] R. Shaheen, L. Han, E. Faqeih, N. Ewida, E. Alobeid, E.M. Phizicky, F.S. Alkuraya, A homozygous truncating mutation in PUS3 expands the role of tRNA modification in normal cognition, Hum. Genet. 135 (2016) 707–713.
[123] H. Najmabadi, H. Hu, M. Garshasbi, T. Zemojtel, S.S. Abedini, W. Chen, M. Hosseini, F. Behjati, S. Haas, P. Jamali, A. Zecha, M. Mohseni, L. Puttmann, L.N. Vahid, C. Jensen, L.A. Moheb, M. Bienek, F. Larti, I. Mueller, R. Weissmann, H. Darvish, K. Wrogemann, V. Hadavi, B. Lipkowitz, S. Esmaeeli-Nieh, D. Wieczorek, R. Kariminejad, S.G. Firouzabadi, M. Cohen, Z. Fattahi, I. Rost, F. Mojahedi, C. Hertzberg, A. Dehghan, A. Rajab, M.J. Banavandi, J. Hoffer, M. Falah, L. Musante, V. Kalscheuer, R. Ullmann, A.W. Kuss, A. Tzschach, K. Kahrizi, H.H. Ropers, Deep sequencing reveals 50 novel genes for recessive cognitive disorders, Nature 478 (2011) 57–63.
[124] M.P. Guy, M. Shaw, C.L. Weiner, L. Hobson, Z. Stark, K. Rose, V.M. Kalscheuer, J. Gecz, E.M. Phizicky, Defects in tRNA anticodon loop 2′-*O*-methylation are implicated in nonsyndromic X-linked intellectual disability due to mutations in FTSJ1, Hum. Mutat. 36 (2015) 1176–1187.
[125] T. Karlsborn, H. Tukenmez, A.K. Mahmud, F. Xu, H. Xu, A.S. Bystrom, Elongator, a conserved complex required for wobble uridine modifications in eukaryotes, RNA Biol. 11 (2014) 1519–1528.
[126] J.S. Cohen, S. Srivastava, K.D. Farwell, H.M. Lu, W. Zeng, H. Lu, E.C. Chao, A. Fatemi, ELP2 is a novel gene implicated in neurodevelopmental disabilities, Am. J. Med. Genet. A 167 (2015) 1391–1395.
[127] C.L. Simpson, R. Lemmens, K. Miskiewicz, W.J. Broom, V.K. Hansen, P.W. van Vught, J.E. Landers, P. Sapp, L. Van Den Bosch, J. Knight, B.M. Neale, M.R. Turner, J.H. Veldink, R.A. Ophoff, V.B. Tripathi, A. Beleza, M.N. Shah, P. Proitsi, A. Van Hoecke, P. Carmeliet, H.R. Horvitz, P.N. Leigh, C.E. Shaw, L.H. van den Berg, P.C. Sham, J.F. Powell, P. Verstreken, R.H. Brown Jr., W. Robberecht, A. Al-Chalabi, Variants of the elongator protein 3 (ELP3) gene are associated with motor neuron degeneration, Hum. Mol. Genet. 18 (2009) 472–481.
[128] S. Laguesse, C. Creppe, D.D. Nedialkova, P.P. Prevot, L. Borgs, S. Huysseune, B. Franco, G. Duysens, N. Krusy, G. Lee, N. Thelen, M. Thiry, P. Close, A. Chariot, B. Malgrange, S.A. Leidel, J.D. Godin, L. Nguyen, A dynamic unfolded protein response contributes to the control of cortical neurogenesis, Dev. Cell 35 (2015) 553–567.
[129] M.P. Cuajungco, M. Leyne, J. Mull, S.P. Gill, W. Lu, D. Zagzag, F.B. Axelrod, C. Maayan, J.F. Gusella, S.A. Slaugenhaupt, Tissue-specific reduction in splicing efficiency of IKBKAP due to the major mutation associated with familial dysautonomia, Am. J. Hum. Genet. 72 (2003) 749–758.
[130] T. Karlsborn, H. Tukenmez, C. Chen, A.S. Bystrom, Familial dysautonomia (FD) patients have reduced levels of the modified wobble nucleoside mcm(5)s(2)U in tRNA, Biochem. Biophys. Res. Commun. 454 (2014) 441–445.
[131] L.J. Strug, T. Clarke, T. Chiang, M. Chien, Z. Baskurt, W. Li, R. Dorfman, B. Bali, E. Wirrell, S.L. Kugler, D.E. Mandelbaum, S.M. Wolf, P. McGoldrick, H. Hardison, E.J. Novotny, J. Ju, D.A. Greenberg, J.J. Russo, D.K. Pal, Centrotemporal sharp wave EEG trait in rolandic epilepsy maps to elongator protein complex 4 (ELP4), Eur. J. Hum. Genet. 17 (2009) 1171–1181.

[132] R. Shaheen, G.M. Abdel-Salam, M.P. Guy, R. Alomar, M.S. Abdel-Hamid, H.H. Afifi, S.I. Ismail, B.A. Emam, E.M. Phizicky, F.S. Alkuraya, Mutation in WDR4 impairs tRNA m (7)G46 methylation and causes a distinct form of microcephalic primordial dwarfism, Genome Biol. 16 (2015) 210.
[133] S. Edvardson, L. Prunetti, A. Arraf, D. Haas, J.M. Bacusmo, J.F. Hu, A. Ta-Shma, P.C. Dedon, V. de Crecy-Lagard, O. Elpeleg, tRNA N6-adenosine threonylcarbamoyltransferase defect due to KAE1/TCS3 (OSGEP) mutation manifest by neurodegeneration and renal tubulopathy, Eur. J. Hum. Genet. 25 (2017) 545–551.
[134] W.R. Farkas, Effect of diet on the queuosine family of tRNAs of germ-free mice, J. Biol. Chem. 255 (1980) 6832–6835.
[135] C. Fergus, D. Barnes, M.A. Alqasem, V.P. Kelly, The queuine micronutrient: charting a course from microbe to man, Nutrients 7 (2015) 2897–2929.
[136] F. Tuorto, C. Legrand, C. Cirzi, G. Federico, R. Liebers, M. Muller, A.E. Ehrenhofer-Murray, G. Dittmar, H.J. Grone, F. Lyko, Queuosine-modified tRNAs confer nutritional control of protein translation, EMBO J. 37 (2018).
[137] T. Rakovich, C. Boland, I. Bernstein, V.M. Chikwana, D. Iwata-Reuyl, V.P. Kelly, Queuosine deficiency in eukaryotes compromises tyrosine production through increased tetrahydrobiopterin oxidation, J. Biol. Chem. 286 (2011) 19354–19363.
[138] S. Varghese, M. Cotter, F. Chevot, C. Fergus, C. Cunningham, K.H. Mills, S.J. Connon, J.M. Southern, V.P. Kelly, In vivo modification of tRNA with an artificial nucleobase leads to full disease remission in an animal model of multiple sclerosis, Nucleic Acids Res. 45 (2017) 2029–2039.
[139] C. Gu, T.J. Begley, P.C. Dedon, tRNA modifications regulate translation during cellular stress, FEBS Lett. 588 (2014) 4287–4296.
[140] I.M. Aparicio-Erriu, J.H. Prehn, Molecular mechanisms in amyotrophic lateral sclerosis: the role of angiogenin, a secreted RNase, Front. Neurosci. 6 (2012) 167.
[141] M.L. Chen, R.M. Wu, C.H. Tai, C.H. Lin, Mutational analysis of angiogenin gene in Parkinson's disease, PLoS One 9 (2014), e112661.
[142] M.J. Greenway, P.M. Andersen, C. Russ, S. Ennis, S. Cashman, C. Donaghy, V. Patterson, R. Swingler, D. Kieran, J. Prehn, K.E. Morrison, A. Green, K.R. Acharya, R.H. Brown Jr., O. Hardiman, ANG mutations segregate with familial and 'sporadic' amyotrophic lateral sclerosis, Nat. Genet. 38 (2006) 411–413.
[143] M.A. van Es, H.J. Schelhaas, P.W. van Vught, N. Ticozzi, P.M. Andersen, E.J. Groen, C. Schulte, H.M. Blauw, M. Koppers, F.P. Diekstra, K. Fumoto, A.L. LeClerc, P. Keagle, B.R. Bloem, H. Scheffer, B.F. van Nuenen, M. van Blitterswijk, W. van Rheenen, A.M. Wills, P.P. Lowe, G.F. Hu, W. Yu, H. Kishikawa, D. Wu, R.D. Folkerth, C. Mariani, S. Goldwurm, G. Pezzoli, P. Van Damme, R. Lemmens, C. Dahlberg, A. Birve, R. Fernandez-Santiago, S. Waibel, C. Klein, M. Weber, A.J. van der Kooi, M. de Visser, D. Verbaan, J.J. van Hilten, P. Heutink, E.A. Hennekam, E. Cuppen, D. Berg, R.H. Brown Jr., V. Silani, T. Gasser, A.C. Ludolph, W. Robberecht, R.A. Ophoff, J.H. Veldink, R.J. Pasterkamp, P.I. de Bakker, J.E. Landers, B.P. van de Warrenburg, L.H. van den Berg, Angiogenin variants in Parkinson disease and amyotrophic lateral sclerosis, Ann. Neurol. 70 (2011) 964–973.
[144] S. Gagliardi, A. Davin, P. Bini, E. Sinforiani, T.E. Poloni, L. Polito, C. Rivoiro, G. Binetti, A. Paterlini, L. Benussi, R. Ghidoni, N. Vanacore, C. Cereda, A novel nonsense angiogenin mutation is associated with Alzheimer disease, Alzheimer Dis. Assoc. Disord. (2018)https://doi.org/10.1097/WAD.0000000000000272 [Epub ahead of print].
[145] D. Kieran, J. Sebastia, M.J. Greenway, M.A. King, D. Connaughton, C.G. Concannon, B. Fenner, O. Hardiman, J.H. Prehn, Control of motoneuron survival by angiogenin, J. Neurosci. 28 (2008) 14056–14061.
[146] W.J. Bradshaw, S. Rehman, T.T. Pham, N. Thiyagarajan, R.L. Lee, V. Subramanian, K.R. Acharya, Structural insights into human angiogenin variants implicated in Parkinson's disease and amyotrophic lateral sclerosis, Sci. Rep. 7 (2017) 41996.
[147] M. Saikia, M. Hatzoglou, The many virtues of tRNA-derived stress-induced RNAs (tiRNAs): discovering novel mechanisms of stress response and effect on human health, J. Biol. Chem. 290 (2015) 29761–29768.
[148] S. Li, G.F. Hu, Emerging role of angiogenin in stress response and cell survival under adverse conditions, J. Cell. Physiol. 227 (2012) 2822–2826.
[149] S. Yamasaki, P. Ivanov, G.F. Hu, P. Anderson, Angiogenin cleaves tRNA and promotes stress-induced translational repression, J. Cell Biol. 185 (2009) 35–42.
[150] L.D.F. Moon, Chromatolysis: do injured axons regenerate poorly when ribonucleases attack rough endoplasmic reticulum, ribosomes and RNA? Dev. Neurobiol. 78 (2018) 1011–1024.
[151] S.M. Lyons, M.M. Fay, Y. Akiyama, P.J. Anderson, P. Ivanov, RNA biology of angiogenin: current state and perspectives, RNA Biol. 14 (2017) 171–178.
[152] P. Ivanov, M.M. Emara, J. Villen, S.P. Gygi, P. Anderson, Angiogenin-induced tRNA fragments inhibit translation initiation, Mol. Cell 43 (2011) 613–623.
[153] X. Wang, Z. Matuszek, Y. Huang, M. Parisien, Q. Dai, W. Clark, M.H. Schwartz, T. Pan, Queuosine modification protects cognate tRNAs against ribonuclease cleavage, RNA 24 (2018) 1305–1313.
[154] H.K. Kim, G. Fuchs, S. Wang, W. Wei, Y. Zhang, H. Park, B. Roy-Chaudhuri, P. Li, J. Xu, K. Chu, F. Zhang, M.S. Chua, S. So, Q.C. Zhang, P. Sarnow, M.A. Kay, A transfer-RNA-derived small RNA regulates ribosome biogenesis, Nature 552 (2017) 57–62.
[155] N.H. Blewett, J.R. Iben, S. Gaidamakov, R.J. Maraia, La deletion from mouse brain alters pre-tRNA metabolism and accumulation of Pre-5.8S rRNA, with neuron death and reactive astrocytosis, Mol. Cell. Biol. 37 (2017).
[156] J. Wan, M. Yourshaw, H. Mamsa, S. Rudnik-Schoneborn, M.P. Menezes, J.E. Hong, D.W. Leong, J. Senderek, M.S. Salman, D. Chitayat, P. Seeman, A. von Moers, L. Graul-Neumann, A.J. Kornberg, M. Castro-Gago, M.J. Sobrido, M. Sanefuji, P.B. Shieh, N. Salamon, R.C. Kim, H.V. Vinters, Z. Chen, K. Zerres, M.M. Ryan, S.F. Nelson, J.C. Jen, Mutations in the RNA exosome component gene EXOSC3 cause pontocerebellar hypoplasia and spinal motor neuron degeneration, Nat. Genet. 44 (2012) 704–708.
[157] E.L. Paley, G. Perry, O. Sokolova, Tryptamine induces axonopathy and mitochondriopathy mimicking neurodegenerative diseases via tryptophanyl-tRNA deficiency, Curr. Alzheimer Res. 10 (2013) 987–1004.
[158] E.L. Paley, G. Perry, Towards an integrative understanding of tRNA aminoacylation–diet–host–gut microbiome interactions in neurodegeneration, Nutrients 10 (2018).