epigenomes

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Review

Epitranscriptome and FMRP Regulated mRNA Translation

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Abstract: An important regulatory mechanism affecting mRNA translation involves various covalent modifications of RNA, which establish distinct epitranscriptomic signatures that actively influence various physiological processes. Dendritic translation in mammalian neurons is a potent target for RNA modification-based regulation. In this mini-review, we focus on the effect of potential RNA modifications on the spatiotemporal regulation of the dendritic translation of mRNAs, which are targeted by two important neuronal translational co-regulators, namely TDP-43 and Fragile X Mental Retardation Protein (FMRP).

Keywords: epitranscriptome; FMRP; TDP-43; RNA methylation; RNA editing; dendritic local translation; neurological diseases

1. Introduction

Genetic study in the last decade has extended beyond exploration of simple DNA coding. Highly regulated structural modifications of DNA and RNA are now believed to act as molecular bridges between genes and the environment and are responsible for several normal and pathogenic phenotypes. Epigenomics ('epi-' is derived from the Greek word meaning 'over' or 'above') defines the study of nucleic acid modifications that interfere with gene copy number, DNA transcription, translation and RNA editing processes. Epigenetic mechanisms include DNA methylation (5-methylcytosine and its oxidized products, namely, 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxycytosine), histone modifications and the actions of non-coding RNAs, e.g., miRNAs. Besides these, another regulatory epigenetic mechanism involves a plenitude of chemical modifications occurring in RNAs that collectively constitute the "epitranscriptome". The advent of high throughput technologies specially, Next-Generation Sequencing platforms, so far allow us to identify 107 RNA modifications majority of which occur in tRNA and rRNAs [1]. Transcriptome-wide RNA modifications mainly include methyl-6-adenosine (m^6A), methyl-5-cytosine (m^5C) and conversion of adenosine-to-inosine (A-to-I). Both m^6A and m^5C occur in mRNAs with m^6A being populated around stop codons [2–4], whereas m^5C marks have been found in tRNAs and a variety of ncRNAs [5,6]. The m^6A is a reversible RNA modification. Adenosine bases can be methylated by Methyltransferase Like protein (METTL)-14 and -3 or m^6A marks on RNAs can be erased by demethylases like Fat mass and Obesity-associated protein (FTO) and Alkb homolog 5 (ALKBH5) [7]. Cytosine methylation of RNAs are catalyzed by m^5C methyltransferases that transfer methyl groups from S-adenosylmethionine (SAM) [8]. The m^5C methyltransferases were divided into four major families: NOP2/NOL1, YebU/Trm4, RsmB, and NSun6 [8,9]. RNA editing, mainly involving A-to-I conversion is also a part of epitranscriptome and catalyzed by adenosine deaminases (ADARs) [10,11]. Besides the above-mentioned conventional RNA modifications, recently other infrequent structural changes in RNAs have been reported,

e.g., pseudo-uridylations (Ψ) in various ncRNAs and mRNAs by Ψ synthases [12,13]. It causes the isomerization of uridine residues [14] and is known to increase the translation efficiency of the modified mRNAs [15]. Another relatively less abundant RNA modification is N^6, 2′-O-dimethyladenosine (m^6A_m) that involves methylation at the 2′-O as well as N^6 positions of adenosine. The m^6A_m modification is generated by methylation of the N^6 position of 2′-O-methyladenosine (A_m) that follows the 7-methylguanosine caps of some mRNAs [16,17]. Different modifications in RNAs have been schematically represented in Figure 1A and described in Table 1. Also chemical structures of modified bases of RNAs and the enzymes catalyzing the reversible/irreversible modification reactions have been shown in Figure 1B. These modifications undoubtedly control many aspects of mRNA translation, and therefore likely control important biological processes such as regulation of circadian rhythms, embryonic stem cell differentiation, neuronal function, and early neuronal, as well as brain development. In this mini-review, we concentrate on m^6A, m^5C, and A-to-I modifications of RNAs in the context of neurological disorders and discuss potential influence of RNA methylation upon dendritic translation of mRNAs targeted by two translational regulators Fragile X Mental Retardation Protein (FMRP) and TDP-43.

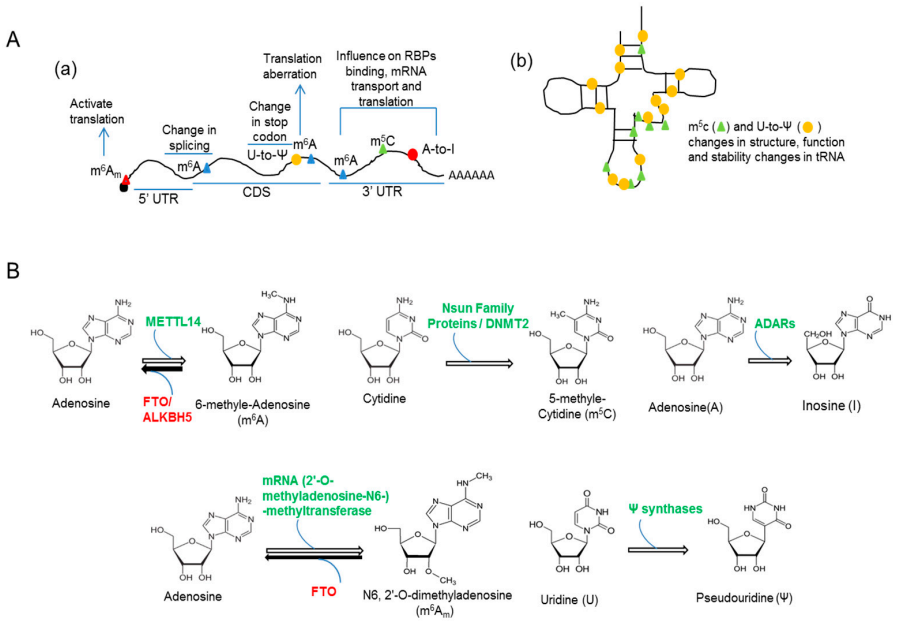

Figure 1. RNA methylation and editing. (**A**) Schematic representation of the presence of m^6A, m^5C, m^6A_m methylation marks as well as deamination (A-to-I) and pseudouridylation (U-to-Ψ) modifications on different parts of mRNA (**a**) and tRNA (**b**); (**B**) Representation of chemical structures of unmodified and modified RNA bases as well as RNA modification enzymes (Table 1).

Table 1. Chemical modifications of different RNAs and associated enzymes.

RNA Modification	Base Involved	Occur in	Modification Enzyme/s
m^6A	Adenosine	mRNA, tRNA	METTL3/METTl14
m^5C	Cytosine	mRNA, tRNA, ncRNAs	NOP2/NOL1, YebU/Trm4, RsmB and NSun family proteins
A-to-I conversion	Adenosine	mRNAs	Adenosine deaminases
m^6A_m	Adenosine	mRNA	mRNA (2′-O-methyladenosine-N6-) methyltransferases
Pseudouridylation	Uridine	ncRNA, mRNA	Ψ synthases

2. RNA Methylation and Neuronal Function

Adenosine methylation (m^6A) has been found to appear copiously throughout transcriptome, and thus target many neuronal mRNAs with subsequent active modulation of the intracellular response

to neuronal signaling events [2,18]. This is directly correlated with the occurrence of the highest levels of m^6A in brain tissue compared to other tissues in mammals. The dynamic nature of m^6A modification is revealed by the experience-dependent and locus specific accumulation of this modification near the stop codons of mRNAs of neural plasticity associated genes in mouse prefrontal cortex [19]. Recent studies have identified two m^6A demethylases [20,21], one of which is FTO that has been reported to be associated with diseases such as cancer [22], obesity [23], attention-deficit hyperactivity disorder [24], and Alzheimer's disease [25,26]. Impaired presynaptic dopamine receptor signaling in dopaminergic neuron was observed after targeted deletion of FTO indicating that it is necessary for the proper presynaptic response to extracellular dopamine levels [27]. Elucidation of mechanisms underlying m^6A-mediated regulation of mRNA function in connection with neuronal signaling events will unfold various other roles of this epitranscriptomic mark in neuronal function.

Bisulfite sequencing and other transcriptome-wide approaches allowed us to identify another widespread RNA modification, m^5C, in coding and non-coding RNAs, such as vault RNAs (vtRNAs) and tRNAs [28,29]. In the case of tRNAs, m^5C modifications affect degradation and ribonuclease cleavage, thus can alter global protein translation [30–34]. Also it has been shown that deposition of m^5C in the vtRNAs regulate correct processing of them to generate a specific set of small RNAs that functionally resemble microRNAs and act upon a specific set of mRNA targets [5]. In rRNAs and mRNAs, m^5C also thought to affect translation [33,35]. Another important function of m^5C deposition in the mRNA is to affect stability of target mRNA [36,37]. In higher eukaryotes deposition of m^5C modification is carried out by RNA methyltransferases NSun2 and DNMT2 [38–40]. NSun2 is a nucleoler protein and encoded by highly conserved family of NOL1/NOP2/Sun domain (NSun) containing RNA methyltransferase genes, which comprises of six members including *NSun2* or *Misu* [39,41]. High expression of NSun2 was found steadily from E7.5 to E10.5 during mouse embryogenesis [42] and its expression has been reported to enrich specifically in the brain [43]. Roles of NSun2 mediated m^5C RNA modification has been reported in tissue development, differentiation, cancer, stem cell differentiation, and cellular signaling [34,39,41,43–49]. Interestingly, mutations in *Nsun2* gene causing loss of mRNA leads to impairment of neurocognitive functions as observed in syndromic autosomal-recessive intellectual disability, Dubowitz-like syndrome and Noonan-like syndrome [44,50–52]. Also Loss of DNMT2 has been implicated in organ development in zebrafish [53,54]. Since m^5C deposition on tRNA directly confers more stability, a loss of NSun2 or DNMT2-mediated m^5C methylation induces, repression of protein translation in eukaryotes, which occurs via stress-induced tRNA cleavage [54–62]. How the loss of methylation causes symptoms of these neurological diseases is not yet fully understood. Loss of tRNA methylation could be the main defect causing these disorders as the vast majority of NSun2 targets are tRNAs [4–6]. Interestingly, increased tRNA cleavage has been implicated in neurodegenerative and neurodevelopmental disorders [63,64] that are commonly associated with oxidative stress [65,66].

3. RNA Editing

RNA editing is the mechanism, which acts upon RNAs post-transcriptionally, to modify specific bases thereby generates RNA and protein diversity. RNA editing includes two chemical modifications, namely, pseudouridylation, that is isomerization of uridine residues or deamination that involves removal of an amine group. The most prevalent form of RNA editing is the deamination reaction involving adenosine (A) to generate inosine (I) in double-stranded RNA. Adenosine-to-inosine conversion takes place at the pre-mRNA level and is catalyzed by the family of RNA-specific adenosine deaminases (ADARs) and subsequently the inosine is recognized as guanosine during translation [10,67–70]. ADARs-catalyzed A-to-I conversation has been implicated in many neurological disorders including depression, epilepsy, amyotrophic lateral sclerosis (ALS), and in several forms of cancer [71,72]. One prominent example citing requirement of RNA editing in brain function showed engineered RNA editing-impaired *GluR-B* allele synthesized calcium-permeable GluR-B subunit of glutamate receptor leading to excess calcium influx into neurons causing postnatal death in mice [73].

The most common RNA modification observed in patients with ALS is deamination of adenosine to inosine [74] and presence of Ca^{2+}-permeable AMPA receptor-mediated pathogenic mechanism causing motor neuron death in ALS has been shown to operate due to reduction of ADAR2 leading to failure of GluA2 RNA editing [75].

4. Dendritic Local Translation and Neurological Disorders

Dendritic localization of mRNAs first hinted that RNA translation might occur locally within the dendrites [76]. Later, other translation related components e.g., initiation and elongation factors, ribosomal proteins, polyribosomes, and tRNAs were also discovered inside dendrites [77]. Further research revealed that dendritic local translation of synaptic mRNAs can be visualized in cultured neurons [78] and it can be stimulated by neuron activation [79–82]. It has also been shown that these mRNAs are transported to dendrites under neuron activity stimulation [83–85] and undergoes translation when they reach the destination [86–88]. Neuron activity-dependent dendritic translation can regulate synaptic plasticity, dendritic spinogenesis [89,90], as well as maintain long lasting changes in dendritic synapses such as Long-Term Potentiation (LTP) and Long-Term-Depression (LTD) [91–93].

In this context, FMRP is required to be mentioned because of its association with neurological diseases and its important role in stimulus-dependent translation and synaptic plasticity [94]. FMRP is a component of ribonucleoprotein complexes (RNPs) that transport mRNAs to dendrites, and it probably plays an active role in this process. This RNA binding protein (RBP) is a well-known translational repressor that inhibits either the initiation or elongation step [95]. Through its RNA-binding domains FMRP can bind mRNAs possessing the G-quadruplex structure and about 4% of total mouse brain mRNAs are known to interact with this protein [96,97]. In a mouse model for Fragile X mental retardation disease, loss of FMRP caused an increased number of dendritic spines [98], impaired brain development and deregulated synaptic plasticity [94] as a consequence of activation of global protein synthesis [99].

Recently, it has been established that FMRP and Frontotemporal Lobar Dementia (FTLD)/ALS pathology related protein TDP-43 physically interact and associate with same mRNPs [100]. A functional link between these two RBPs in dendritic translation regulation has also been elucidated [100,101]. In another study, overexpression of TDP-43 inhibited translation of Futsch (*Drosophila* homolog of Map1b) mRNA in motor neurons [102], which was re-activated by overexpression of FMRP [103]. Moreover, 1140 common mRNA targets of FMRP and TDP-43 have been identified. Among them 160 targets are related to neuron structure, function, and neuron development. A significant portion of these mRNAs might be co-regulated by FMRP and TDP-43 at the translational level. Interestingly, the above mentioned 160 common targets of FMRP and TDP-43 also include candidate genes for Autism Spectrum Disorder (ASD; e.g., *Rac1, Mapk1, Reln,* and *Shank3*), Alzheimer's disease (AD; e.g., *Ank1, App,* and *Apoe*) and Schizophrenia (e.g., *Grin2b* and *Gsk3b*) indicating that loss-of-function of either of these two RBPs might develop similar phenotypes [100].

5. Potential Roles of RNA Modifications in TDP-43/FMRP-Associated Neurological Diseases

As described above, FMRP and TDP-43 probably play important roles in modulating both neurodevelopmental (e.g., ASD, Schizophrenia) and neurodegenerative (e.g., AD) disorders by co-regulating dendritic local translation. It has been established that TDP-43 recruits the FMRP-CYFIP1-eIF4E inhibitory complex to the target mRNAs present at dendrites, thereby repressing initiation of translation [100]. Thus TDP-43 acts as an adaptor protein between target mRNAs and FMRP. Upon relevant synaptic stimulation, FMRP is dephosphorylated [104] and either FMRP-CYFIP1 is dissociated from eIF4E [105] or FMRP is dissociated from mRNAs, leading to re-activation of dendritic local translation [106]. However, it remains elusive how distinct sets of mRNAs are translationally regulated by FMRP/TDP-43 in the context of different neurological disorders. Also, underlying mechanisms that elicit differential responses in different regions of the brain under same pre-synaptic signals are not fully conceived. Here, it is intriguing to speculate that alike epigenetic

code mediated regulation of gene transcription, the epitranscriptomic code drives evolution of dynamic modes of translational regulation in post-mitotic neurons via installation of potentially reversible RNA modifications such as methylation/demethylation of mRNAs, tRNAs and rRNAs [107–110].

In this context, the m^5C methylation of the RNAs by NSun2 is of great importance for fine-tuning in dendritic local translation as well as for neuronal function. This methylase is associated with human intellectual disability syndromes, ASD, and epilepsy [44,50–52,111]. *Drosophila* and mouse models with down regulated NSun2 showed significant problems with learning and memory [44,112]. Interestingly, the hippocampus region of the mouse brain showed the highest expression of NSun2 [112,113]. NSun2-deficient mice also showed fragmentation of tRNAs followed by stress responses and apoptosis of neurons [112], a significant decrease in global translation [34], and mis-regulation of miRNAs that are known important regulators of translation along with RBPs [114]. Many indirect evidences could be put forward in support of the notion that NSun2-mediated methylation may regulate dendritic local translation and neurodevelopmental diseases. For example, NSun2 partially co-localizes with FMRP in dendrites but, in axons, no appreciable co-localization of this RNA methylase with FMRP has been detected [115]. Also a significant overlap between mRNA targets of FMRP and NSun2 has been reported [115]. Among different methylation targets of NSun2, mTOR mRNA is of particular interest, because of its activity-dependent translational up regulation in dendrites that facilitates phosphorylation of 4E-BP (eIF4E binding protein, e.g., CYFIP1) and release of CYFIP1-FMRP-TDP-43 mediated translational repression [116,117]. The potential role of mTOR mRNA methylation on synaptic mRNA translation co-regulated by TDP-43 and FMRP is schematically represented in Figure 2 (right schemes).

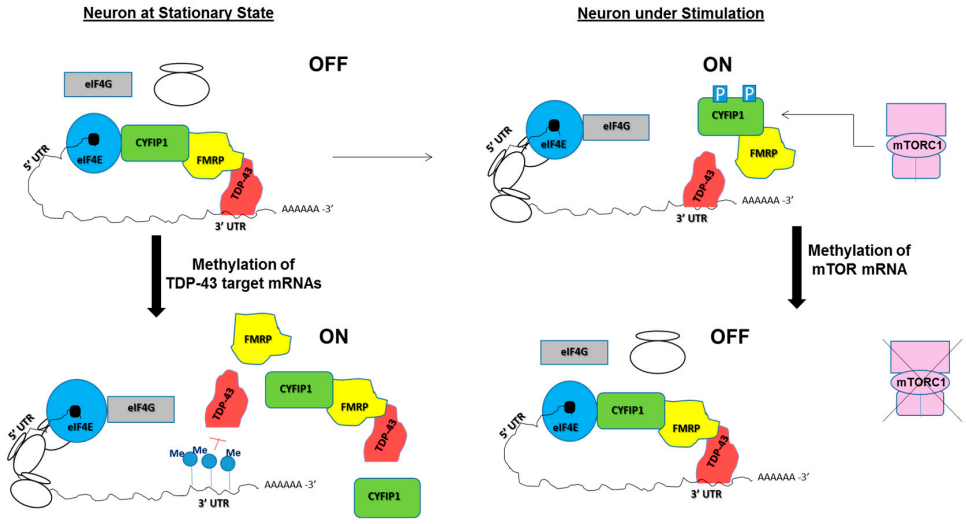

Figure 2. A model showing potential roles of RNA methylation on spatiotemporal translational control of mRNAs, co-regulated by TDP-43 and FMRP. (**Left**) In the stationary state of immature neurons FMRP (yellow) or the FMRP-CYFIP1 complex is recruited to the vicinity of the mRNA(s) by mRNA-bound TDP-43 (red). CYFIP1 (green) interacts with eIF4E (blue) and blocks eIF4G (grey) to bind with eIF4E and to form the translation initiation complex eIF4F (not shown). Thus, translation of synaptic mRNAs like Rac1 mRNA remain in "OFF" state (top left scheme). Methylation marks at the 3′UTR region of mRNAs targeted by TDP-43 may inhibit its interaction with TDP-43 and thus potentially block the recruitment of CYFIP1-FMRP complex to these mRNAs. This leads to initiation of translation marked as "ON" state (lower left scheme); (**Right**) in neurons under stimulation, mTOR pathway is activated and mTORC1 (purple) phosphorylates CYFIP1 that inhibits eIF4E/CYFIP1-FMRP-TDP-43 interaction. Thus translation machinery becomes "ON" (top right scheme). The mTOR mRNA methylation-induced inhibition of mTOR pathway may influence its downstream signaling events at neuronal synapses (e.g., phosphorylation of CYFIP1 protein), to inhibit translation initiation resulting in the "OFF" state even under stimulation (lower right scheme).

Interestingly, NSun2-mediated m^5C methylation of ncRNAs regulates cellular levels of the transmembrane AMPA receptor regulatory protein, CACNG8 [5]. The point to be noted here is that the transmembrane AMPA receptor subunit is important in TDP-43-mediated spinogenesis [101]. Lastly, NSun2 mRNA forms an in vivo complex with the TDP-43-associated protein, FUS, indicating the presence of a complex mechanism involving different RNA metabolism pathways [118]. The potential role of m^6A residues in dendritic localization and stability of ASD associated mRNAs have been recently reviewed [119]. Although there is no direct evidence of m^6A methylation affecting TDP-43/FMRP-regulated neuronal translation or neurological disorders, it should be noted that in human cells more than 12,000 m^6A sites in about 7000 mRNAs have been identified [119] and the most of m^6A RNA methylation found in the last exons. This might influence 3′-UTR-mediated translational regulation of mRNAs [120,121]. Therefore, m^6A methylation potentially exerts fine-tuning on the dendritic translation mechanisms by inhibiting mRNA binding of TDP-43 at the 3′UTR region. This probably would affect TDP-43 mediated mRNA recruitment to a translation inhibitory complex. A recent study, examining the consensus RNA-binding sites of FMRP protein, speculated the role of m^6A as the negative determinant of FMRP-binding to target mRNAs [122]. Schematic representation of potential role of RNA methylation on spatiotemporal translational control of mRNAs co-regulated by TDP-43 and FMRP has been shown in Figure 2 (left schemes).

In addition to RNA methylation, aberrant A-to-I RNA editing by adenosine deaminase enzyme in ADAR2-KO mice caused mis-localization and aggregation of TDP-43 [123] and delayed death of motor neurons. It is also reported that motor neurons from ALS patients are more susceptible to RNA-editing deficiencies [124]. Finally, an example of translational regulation at synapses due to 2′-O-methylation of RNA altering the BC1-FMRP interaction with target mRNA [125] indicates the importance of studying non-conventional RNA modifications and their roles in regulating the dendritic translation mechanism in neurons.

As we have described above, RNA modification may play a very important role in dendritic mRNA translation. Several RNA-modifying enzymes exist, and they probably regulate different types of RNA modifications. Systematic study of these enzymes may reveal a complexity long postulated for RNA and its involvement in neurological diseases.

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