RNA Modifications and RNA Metabolism in Neurological Disease

The intrinsic cellular heterogeneity and molecular complexity of the mammalian nervous system relies substantially on the dynamic nature and spatiotemporal patterning of gene expression. These features of gene expression are achieved in part through mechanisms involving various epigenetic processes such as DNA methylation, post-translational histone modifications, and non-coding RNA activity, amongst others. In concert, another regulatory layer by which RNA bases and sugar residues are chemically modified enhances neuronal transcriptome complexity. Similar RNA modifications in other systems collectively constitute the cellular epitranscriptome that integrates and impacts various physiological processes. The epitranscriptome is dynamic and is reshaped constantly to regulate vital processes such as development, differentiation and stress responses. Perturbations of the epitranscriptome can lead to various pathogenic conditions, including cancer, cardiovascular abnormalities and neurological diseases. These RNA modifications modulate the stability, transport and, most importantly, translation of RNA.

1. Introduction

RNA is subjected to multifaceted regulatory processes to sustain diversity and complexity at the organismal and molecular levels. It has evolved to participate in diverse cellular processes owing to its capability to couple enzymatic activity with the storage and transfer of information. Upon being transcribed, the nascent RNA is subjected to various processing mechanisms, collectively termed post-transcriptional processing, that ultimately confer it with its information storage/transfer and regulatory functions. Post-transcriptional processing of eukaryotic RNA typically includes 5′ capping, intron removal or splicing, and addition of a 3′ polyadenylated tail. Another crucial mechanism of post-transcriptional RNA modification is the chemical modification of RNA bases and sugar residues on the RNA backbone. Similar to chemical modification of DNA cytosine residues that constitute part of the epigenome, chemical modifications of RNA, the "epitranscriptome", adds another regulatory layer to organismal transcriptome-wide complexity. The functional impact of the epitranscriptome manifests in almost all tissues, but it is most apparent in regulating complex organs such as the brain. It is both transcriptomic and epitranscriptomic diversity that endows the nervous system with its complexity, with the latter altering various layers of RNA metabolism. RNA metabolism encompasses diverse processes including biogenesis, transport, splicing, stabilization, storage, and translation. Many recent studies have highlighted how dysregulation of RNA transport, splicing, stabilization, translation, or miRNA/tRNA biogenesis contributes to age-related neurodegenerative diseases [1] and neurodevelopmental disorders [2][3]. Precise spatial and temporal expression of various proteins is essential for appropriate brain development, which is achieved by proper accomplishment of RNA stabilization, transport and translation [4]. Even in the adult brain, RNA metabolism is one of the most crucial mechanisms for maintaining correct brain functions and learning-based memory consolidation [4]. Although different aspects of RNA metabolism contribute to neurodegenerative diseases and neurodevelopmental disorders, RNA-binding proteins (RBPs) play important roles in both kinds of disease pathogenesis [2][5].

2. RNA Metabolism-Associated Neurological Disease Mechanisms

2.1. mRNA Splicing

Introns of pre-mRNAs are removed and exons are joined in a process called pre-mRNA splicing to form mature mRNAs, and this process is regulated by several *cis*-acting elements and via formation of a multi-protein complex termed the spliceosome [6]. The involvement of different *cis*-acting elements alters exon recognition by spliceosomes, giving rise to alternatively spliced mRNAs from the same mRNA transcript. Alternative splicing not only contributes to diversity among species, but also enables tissue-specific expression of differentially spliced products to perform different functions [7].

mRNA splicing is emerging as a crucial mechanism for maintaining neuronal transcriptome complexity, shaping neuronal structure, function, and differentiation processes [7][8][9]. Perturbations of the essential association between *cis*-acting elements and splicing motifs result in splicing defects, potentially resulting in neurological disorders or neurodegenerative disease [10].

Effect on neurodevelopmental diseases: Approximately 1.4% of autism spectrum disorder (ASD) cases are caused by splicing defects [11]. Changes in splicing patterns of several mRNAs related to the PTEN signaling pathway have been observed in a murine model of ASD [12]. Animal models of neurodevelopmental disorders have also revealed alterations to the expression of position-dependent splicing factors. For example, neuro-oncologic ventral antigen (NOVA) and RNA-binding protein FOX (RBFOX) paralogs are positive regulators of exon inclusions during splicing of mRNAs linked to brain development, spine formation and neurite growth, and their downregulation has been observed in post-mortem brain tissue of autistic patients. Polypyrimidine tract-binding protein 1 (PTBP1) is a negative regulator of exon inclusion, and it is highly expressed during early embryonic development when it facilitates cells to enter the neuronal lineage. Abnormal (low) expression of this protein has been linked to schizophrenia-associated seizures [6].

Effect on neurodegenerative diseases: Alternative splicing also regulates the expression of different isoforms of α-synuclein, the main component of Lewy bodies and a hallmark of Parkinson's disease (PD) [13]. Similarly, the ratio of alternatively spliced products of the *tau* gene product MAPT [10], namely 3R tau (formed upon exclusion of exon 10) and 4R tau (formed upon inclusion of exon 10) contribute to another well-known neurodegenerative disorder, Alzheimer's disease (AD). Some recent studies have also highlighted alternative splicing and splicing defects as contributory mechanisms of different neurodegenerative diseases [14]. For instance, a TDP-43 mutation linked to ALS alters the splicing function of TDP-43, resulting in changed RNAs and contributing to early manifestation of the disease [15]. Splicing defects have been established as one of the major contributors for Huntington's disease (HD) [16].CAG repeat expansion in SCA type 6-linked genes induce altered mRNA splicing patterns that result in accumulations of disease-causing polyglutamine-containing protein [17].

2.2. mRNA Alternative Polyadenylation

The alternative polyadenylation (APA) of mRNAs is the use of multiple polyadenylation sites in primary transcripts and in conjunction with alternative splicing. APA expands cellular transcriptomic diversity by generating distinct mRNA isoforms [18]. Depending on the location of polyadenylation sites (PASs), APA can be classified into two types: UTR-APA and coding region-APA (CR-APA) [19]. The presence of APA sites in 3′-UTRs of mRNAs generates transcript isoforms with the same coding region but with different lengths of 3′-UTR regions, thus giving rise to distinct interactions of mRNA isoforms with RNA-binding proteins and non-coding RNAs like microRNA and lncRNAs [18]. On the other hand, CR-APA directly affects the coding region and leads to the generation of proteins with different C-termini [20][21]. APA is found in all eukaryotes, and in mammals, about 70% of all mRNA-encoding genes undergo APA [22][23][24]. APA events can be tissue-specific to a great extent; for example, in the case of 3′-UTR APA isoforms, distal PASs are enriched in neurons, while blood cells and testis tissue favor the use of proximal PASs [25][26]. The functional consequences of APA sites in 3′-UTR of pre-mRNAs are diverse. For example, 3′-UTR-APAs participate in post-transcriptional gene regulation through various methods, such as modification of mRNA stability, translation, nuclear export and cellular localization. The influence of 3′-APA upon stability of mRNAs can be exemplified through altered effects of miRNA functions. For example, about 10% of all miRNAs targeting two cell types can be influenced by expression of APA isoforms [27]. Another way through which 3′-UTR APA events can modulate mRNA stability is differential binding of various RNA binding factors as well as lncRNAs that can affect the mRNA decay process [18]. The localization of mRNAs can also be influenced by 3′-UTR APA events, which is best exemplified in the case of *BDNF* transcripts, where the short isoform is restricted to the cell body while the long isoform is predominantly found in the dendrites [28]. Lastly, 3′-UTR APA events can directly influence protein localization, as evidenced in the case of proteins like CD47, CD44, α1 integrin (ITGA1) and TNF receptor superfamily member 13C (TNFRSF13C) [29]. CR-APA events are known to contribute to protein diversification, as seen in the case of transcripts encoded by genes like calcitonin-related polypeptide-α (*CALCA*) and immunoglobulin M heavy chain (*IgM*) [18]. CR-APA can also repress gene expression by generating severely truncated transcripts through utilization of PAS proximal to the promoter, as observed in the case of transcripts encoded by the mammalian polyadenylation factor cleavage stimulation factor 77 kDa subunit (*CstF-77*) gene [30].

Effect of neurodevelopmental diseases: Neuronal commitment at the early stages of neurodevelopment is heavily influenced by the transcriptome repertoire of neural stem cells. During neurodevelopment, APA contributes significantly to the specification of neuronal lineage in association with other mechanisms such as microRNA networks, alternative splicing, non-sense mediated RNA decay, etc., that shape the transcriptome diversity of neural stem cells. APA events are known to be enriched in specific neuronal cell types [31][32]. Additionally, single-cell RNA sequencing data analysis identified cell type-specific APA landscapes in different GABAergic interneurons in the mouse cerebral cortex.

Interestingly, genes with cell type-specific APA events are enriched in biological processes like synaptic vesicle recycling, neurotransmitter release, ion transport etc., which implies a significant role of APA in synaptic communication and neuronal identity determination [33]. Furthermore, the role of APA during early stages of neurodevelopment, such as the commitment and differentiation of neural progenitors, has been investigated by Grassi et al. where transcriptome-wide changes of 3′-UTR lengths were observed during differentiation of mouse-adherent neural stem cells into GABAergic inhibitory neurons [34]. A group of studies have linked APA events and 3′-UTR in specific genes like *MeCP2*, *FMR1* to disorders with autistic phenotypes such as Rett syndrome, Fragile X-associated syndrome, autism, schizophrenia and other psychiatric diseases [35][36][37][38][39]. Since ASDs have been correlated with aberrations of calcium signaling, the dysregulation of APA events in the autistic brains, as found by analyzing RNA sequencing data from publicly available databases, are linked with dysregulation of calcium ion homeostasis by Szkop et al. [40]. The effect of APA in the regulation of MeCP2 protein levels and concomitant development of neuropsychiatric diseases has been studied by Gennarino et al., where copy-number variation of the *NUDT21* gene that encodes a subunit of pre-mRNA cleavage factor Im is reported to regulate the length of *MeCP2* transcript 3′-UTR [41].

Effect of neurodegenerative diseases: The ability of APA events to generate transcripts with varying lengths of 3′-UTR gives rise to their intimate association with the regulation of gene expression. Since significant alterations of gene expression have been observed in neurodegenerative disorders [42][43], APA can be viewed as a potentially important regulatory mechanism operating during the development and progression of different neurodegenerative diseases. Analysis of RNA sequencing data from AD, PD and ALS patients and matched healthy controls, available in public databases, revealed disease-specific changes of APA profiles in a subset of genes among each disease [44]. Although this study found APA profile changes in relatively small subset of genes, and affected genes differ among RNA-sequencing datasets, they found, in all three disease-associated datasets, overrepresentation of genes associated with protein turnover and mitochondrial function. Usage of the distal PAS site in α-synuclein mRNA generates an extended transcript isoform which is shown to be associated with PD development, and the presence of this extended 3′-UTR promotes accumulation of the α-synuclein protein, which gets redirected away from the synaptic terminal towards mitochondria [45]. Genome-wide usage of proximal PAS within 3′-UTR regions or PAS within introns leads to transcriptome-wide shortening of 3′-UTR regions, and that may underlie the development of neurological disorders like oculopharyngeal muscular dystrophy (OPMD) [46].

2.3. mRNA Transport and Translation

Owing to the presence of extended neuronal processes, such as long axons and dendrites, it requires more energy and time to transport proteins on demand from the soma to distal parts of neurons. However, mRNAs are transported along neurites together with ribosomes and all the translation machineries, so mRNAs are ready to be translated in different parts of neurons [47]. Recent investigations have found that ribosomes are assembled at the distal end of axons instead of being formed from proximally translated ribosomal proteins and transported as part of mRNP complexes to the distal site [48][49]. Moreover, various mRNAs can be transported together, yet remain translationally repressed. RBPs play important roles in both mRNA transport and translational repression. Dysregulation of dendritic mRNA transport/translation causes aberrant spine formation and dendritic structural anomalies, as well as learning memory impairments, that are symptoms of neurodevelopmental disorders [50].

Effect on neurodevelopmental diseases: An impressive body of work has uncovered how translational dysregulation of mRNAs is linked to ASD and Fragile X syndrome (FXS) [51]. Most of the experimentally-validated mRNAs (e.g., *Map1b*, *GluR1*, *Rac1*, *CamKII*, *Shank3*, *Gabrb1*, among others) are targets of the RBP Fragile X mental retardation protein (FMRP) and are associated with synaptic structural anomalies and dysfunction, as well as impairments of long-term memory formation [51][52][53]. Furthermore, genetic mutations of several core translation regulatory proteins, e.g., RPL10, eIF4E, UPF3B, GW182, CYFIP1, Caprin1, eIF2B, and PTEN, have also been linked to ASD and other neurodevelopmental disorders such as infantile epilepsy, mental retardation, schizophrenia, attention deficit hyperactivity disorder (ADHD) and many more. More than 1000 such genes have been included in the Simons Foundation Autism Research Initiative (SFARI) database (https://gene.sfari.org/; accessed date July 2021). Further research is in progress to establish the molecular mechanisms underlying translational dysregulation of the mRNA targets of these proteins [54].

Effect on neurodegenerative diseases: Patients suffering spinal muscular atrophy (SMA) exhibit reduced binding of survival motor neurons (SMN) to small nuclear RNA (snRNAs) because of genetic mutation-driven impairment of SMN protein stability, resulting in abnormal snRNA trafficking and maturation [55]. In contrast, ALS-linked mutations enhance stress granule formation or cause aberrant clearance, resulting in larger RNA-protein assemblies [56]. These examples indicate that either hyper- or hypo-assembly of mRNPs causing aberrant transport of mRNAs can lead to many neurodegenerative diseases [55]. Atypical transport/translation of mRNAs associated with the muscleblind-like (MBLN) group of proteins causes myotonic dystrophy (DM) [57]. RAN translation in the *c9orf72* gene harboring G4C2 repeat

expansion mutations at intron 1 has been established as the main cause of ALS and FTLD diseases [58]. In SCA31, expansion of a TGGAA repeat in the BEAN1 transcript causes accumulation of pentapeptide repeat protein translated from all three reading frames using a similar mechanism. Moreover, a UGGAA repeat containing an abnormally structured RNA, known as an RNA foci, sequesters RBPs, affecting their functions and thus contributing to disease phenotypes [59]. RNA foci and the activation of RAN translation are also implicated in SCA8, HD and many other triplet repeat disorders [60] [61]. Recently, mutant huntingtin protein was shown to stall ribosomes, thereby affecting the translation of several mRNAs (including *Mfsd10* and *Ppbp*) that contribute to HD progression [62]. Deviant axonal transport of mRNAs associated with TDP-43 (*Map1b*, *Nefl*) or with FUS (e.g., *Fosb*) contributes to ALS and frontotemporal lobar degeneration (FTLD) [63][64]. Interestingly, translational activation of CyclinD1 and TDP-43 mRNAs via Ataxin2-mediated polyadenylation in association with the Poly-A binding protein PAPD4 can induce TDP-43 proteinopathies, such as the Tau aggregation typical of FTLD, ALS, and AD [65][66]. Together, this evidence establishes dysregulated mRNA transport/translation as a crucial factor in several neurological diseases.

2.4. mRNA Stability

To maintain RNA homeostasis, mRNAs transcribed inside the nucleus decay through various biological processes directed by *cis*-acting elements. Exonucleases and endonucleases contribute to these decay processes [67]. Methylation capping at the 5′ untranslated region (UTR) and polyadenylation at the 3′-UTR protect mRNAs from degradation by these nucleases. Gene expression levels are dependent on mRNA stability, which is measured by the half-lives of mRNAs [68]. mRNA half-life can be increased or decreased by diverse mechanisms [69]. Alternatively spliced mRNAs can harbor or exclude *cis*-acting elements or enable alternative polyadenylation, thereby regulating the stability of the mRNA [70].

Effect on neurodevelopmental diseases: The Hu/Elav group of proteins exert an important role in exon inclusion and differential polyadenylation to alter the stability of mRNAs such as *Bdnf* and *Nf1*, thus regulating neuronal differentiation and function [71]. HuD-null mice exhibit sensory and motor neuron defects [72]. Moreover, neuronal Elav-like (nELAVL) protein has been associated with ASD [73]. Reduced expression of the mRNA stability-related protein RBFOX1 has also been linked to ASD [4]. Recent experimental evidence has further confirmed that FMRP can alter ASD-related mRNA stability to counter Ataxin2-mediated changes in gene expression under different kinds of cellular stress [74].

Effect on neurodegenerative diseases: nELAVL-mediated changes in mRNA stability have also been implicated in neurodegenerative diseases such as AD and PD [75]. A recent study reported that Ataxin2 endows stability on its mRNA target TDP-43, with this function being dependent on its poly-Q domain. Expansion of the poly-Q domain of Ataxin2 alters TDP-43 mRNA stability, resulting in tau protein aggregation and ALS pathogenesis [76]. Another RBP, RBFOX, stabilizes mRNAs encoding synaptic transmissions, and its dysregulation has been linked to AD [77]. Proteins primarily known to regulate other forms of RNA metabolism are also known to alter RNA stability. For instance, TDP-43 participates in stabilizing β-adducin (Add2) mRNA. This phenomenon is predicted to be associated with ALS and FTLD diseases, though its exact mechanism is not yet understood [78]. Thus, different RBPs work together to maintain mRNA/protein homeostasis in the cell by changing mRNA stability and translation. Any failure in this coordinated effort can induce neurological pathogenicity.

2.5. miRNA Biogenesis

Micro-RNAs (miRNAs) are small non-coding regulatory RNAs that post-transcriptionally silence specific mRNAs, representing another form of temporal gene expression control. These miRNAs are involved in fine-tuning gene expression required for neural development, structure and function, so aberrant miRNA activity can induce neurological disease [79]. miRNA profiling has revealed that a considerable number of miRNAs are expressed in the hippocampus of the adult brain in an activity-dependent manner. For instance, miR-132 is expressed under KCl- or DHPG-driven neural activation, and miR-212 is regulated via the CREB activation pathway [80][81].

Effect on neurodevelopmental disease: miRNA biogenesis has been implicated in synaptic plasticity and long-term memory formation [79]. Dysregulated miRNA synthesis and maturation contribute to ASD, intellectual disability, and schizophrenia [82].

Effect on neurodegenerative diseases: Interestingly, the progression of neurodegenerative diseases also appears to be dependent on the differential expression of miRNAs. Post-mortem AD brains display significantly different miRNA expression profiles compared to age-matched controls [83][84]. Specifically, reduced expression of miR-9 in the hippocampus and miR-107 in the cortex were observed in AD brains, and this feature was linked to aberrant expression of BACE1, Sirtuin1, and PSEN1. In contrast, miR-7, miR-153, miR-34b, miR-224, and miR-379 regulate accumulation and aggregation of α-synuclein, a hallmark of PD [85]. ALS-linked inflammation has been linked to dysregulation of miR-577,

miR-155, and let-7 [86]. Moreover, miRNA expression and functions may also be partially responsible for other neurodegenerative diseases such as HD and MD [87][88].

Different RNA metabolisms described above are also shown in **Table 1**.

Table 1. Dysregulated RNA metabolism in neurological diseases.

Disease Type	Altered RNA Metabolism Pathway	RBP(s) Involved	Mechanisms	Neurological Disease(s)	References
Neuro developmental diseases	Splicing, Translation	CPEB4	Missplicing of *CPEB4* causes reduced inclusion of a neuron-specific microexon, leading to diminished expression of the *Cpeb4* transcript that activates translation of mRNAs via polyadenylation under normal conditions	ASD	[89]
	Splicing Translation, mRNA stability, miRNA biogenesis	RBFOX1, RBFOX2 (RBM9), RBFOX3 (Neun)	RBFOX1 binds to the 3′-UTR of its target mRNAs and regulates: - Splicing of *Camk2d* and *Camk2g* mRNAs; - Stability of *Camk2a*, *Camk2b*, *Camk4*, and *Ppp3r1* mRNAs; - translational regulation by RBFOX2 and RBFOX3 (repression) - miRNA biogenesis. Altered splicing of RBFOX family proteins impairs their control of gene expression	ASD	[20][90][91][92]
	Transport, Translation	FMRP	CGG repeat expansion beyond 200 (>200) at the 5′-UTR of *FMR1* affects protein expression, resulting in dysregulated spatio-temporal transport/translation of dendritic mRNAs	FXS	[54]
	APA	NUDT21	Elevated amount of NUDT21, a subunit of pre-mRNA cleavage factor Im, due to copy number variation causes abnormal usage of polyadenylation sites, resulting in the generation of an inefficiently translated long isoform of MeCP2 protein.	Neuropsychiatric disease	[41]

Disease Type	Altered RNA Metabolism Pathway	RBP(s) Involved	Mechanisms	Neurological Disease(s)	References
Neuro degenerative diseases	Splicing	PRPF8	Mutated Huntingtin (HTT) traps PRPF8 (a splicing factor) to cause *CREB1* mis-splicing	HD	[15]
	Translation	HTT	Mutant HTT stalls ribosomes	HD	[62]
	Splicing	MBNL family proteins	RNA corresponding to expanded microsatellite repeats in *DMPK* traps MBNL-family proteins, impairing their normal function in splicing	DM	[93]
	Translation	ATAXIN-2	CAG expansion in the reading frame of *ATAXIN-2* causes loss of protein function that, under normal conditions, acts as an mRNA translation activator via polyadenylation	SCA2, ALS	[65]
	RAN Translation, Abnormal RNA structure (RNA foci)	Matrin-3	GGGGCC repeat expansion mutation in the *C9orf72* gene causes sequestration of Matrin-3 at the RNA foci and RAN translated peptides and loss of function of Matrin-3	FTLD, ALS	[94]
	mRNA stability, Splicing, Translation	nELAVL	nELAVL regulates disease-specific splicing of the pre-mRNAs *Picalm* and *Bin1* by incorporating exons 13 and 6a, respectively. The proteins corresponding to these spliced isoforms have been implicated in trafficking of amyloid precursor protein	AD	[95]

Disease Type	Altered RNA Metabolism Pathway	RBP(s) Involved	Mechanisms	Neurological Disease(s)	References
	Transport, Translation, miRNA biogenesis	TDP-43	- TDP-43-mediated axonal transport/translation of mRNAs such as *Nefl* and *Map1b* is adversely affected in diseased neurons expressing disease-specific mutant TDP-43; - TDP-43 has been implicated in FMRP co-regulation of mRNA transport/translation; - Nuclear localization of TDP-43 is affected in diseased neurons, altering its RNA-binding ability and the fate of target RNAs; - Normal TDP-43 function in cleaving certain pre-miRNAs via Drosha binding in the nucleus is impaired.	FTLD, ALS	[53][96][97][98]
	Transport, Translation	FUS	Normal FUS functions such as axonal transport/translation of mRNAs are adversely impacted in diseased neurons. Under disease conditions, the altered intracellular localization of FUS disrupts its functions as an RBP	FTLD, ALS	[99]
	Splicing, miRNA biogenesis	hnRNPs, MBNL1	mRNA corresponding to shorter CGG repeat expansions (<200) in the 5′UTR of *FMR1* sequester many RBPs, e.g., hnRNPs and MBNL1	Fragile X-associated tremor/ataxia syndrome (FXTAS)	[100]
	APA	α-synuclein	Presence of an extended 3′-UTR region in α-synuclein transcript impacts accumulation of α-synuclein protein that is redirected away from synaptic terminals towards mitochondria	PD	[45]

UTR—untranslated region; hnRNPs—heterogenous nuclear ribonuleoproteins.

2.6. Roles for RBPs in RNA Metabolism and Neurological Diseases

Various mechanisms of RNA metabolism temporally regulate the protein expression responsible for brain development, structure and function. RBPs fine-tune RNA metabolism, resulting in further complexities of gene expression in different neuronal parts [5]. Expression-mediated RBP functions may be countered by other RBPs, thereby maintaining a balance of RNA metabolism and gene expression for neurons in different parts of the brain. Dysregulated RBP functioning and

enrichment can severely perturb such control mechanisms, resulting in neurodevelopmental or neurodegenerative diseases (summarized in **Table 1**) [101][102].

3. RNA Modifications that Change RNA Metabolic Processes

Despite hundreds of RNA modifications on coding and non-coding RNAs having been identified to date, only a few have been studied extensively or linked to disease. Well-studied RNA modifications include the methylation of adenosine at position 6 (m6A, also known as N6-methyladenosine), N1-methyladenosine (m1A), 5-methyl cytosine (m5C), pseudouridine, and RNA editing, e.g., A-to-I (see **Figure 1**) [103][104].
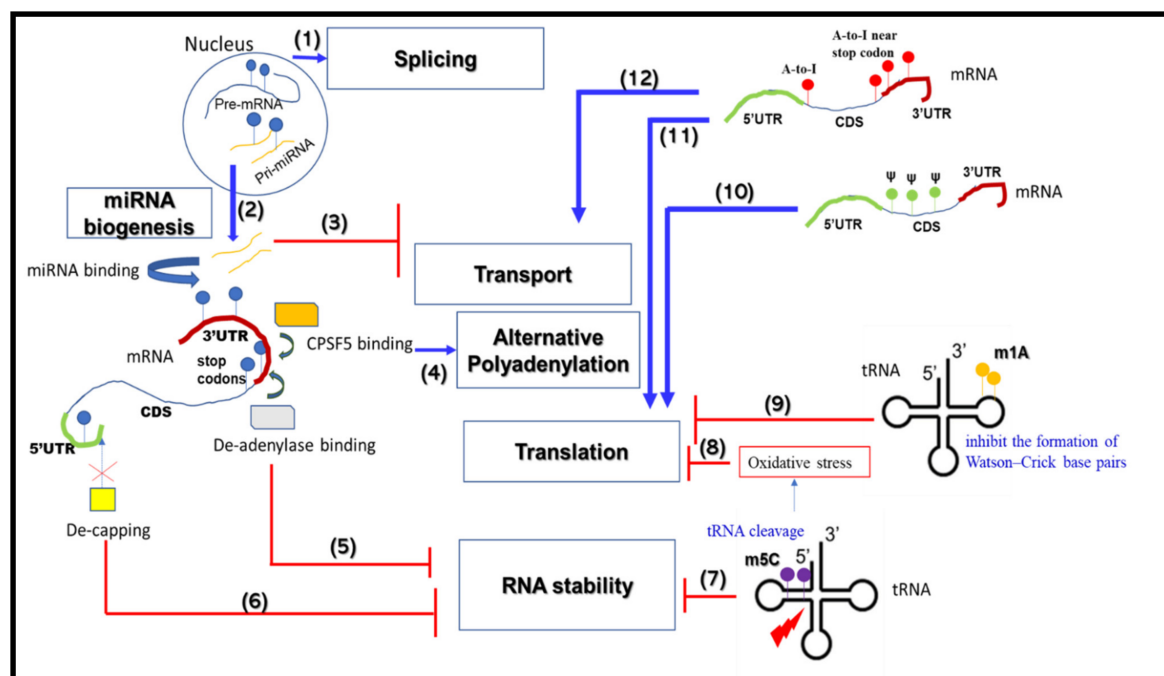

Figure 1. Illustrative model summarizing how various RNA metabolic processes are modulated by RNA modifications. Different RNA modifications, e.g., m6A, m5C, m1A, A-to-I RNA editing and pseudouridine, are represented by blue, purple, yellow, red and yellow colored pins, respectively. Various mechanisms of activation or inhibition of RNA metabolisms by RNA modifications are represented by (**1**) to (**12**), e.g., m6A modifications of pre-mRNAs (**1**) and miRNAs (**2**) facilitate splicing and miRNA biogenesis, respectively. The model shows that m6A modification of the 3′-UTR of mRNAs facilitates binding of miRNAs to this region and inhibits mRNA transport/translation (**3**). VERMA-mediated m6A modification near the 3′-UTR and stop codons of mRNAs facilitates alternative polyadenylation (**4**). Alternatively, m6A modification near the 3′-UTR and stop codons causes de-adenylase binding, thereby impairing stability (**5**). De-capping at the 5′-cap site with nearby m6A inhibits translation initiation and also reduces mRNA stability as a result of endonuclease activity (**6**). m5C modification of tRNAs induces their cleavage, thus altering RNA stability (**7**). Accumulations of cleaved tRNA fragments induce oxidative stress, which inhibits cellular translation (**8**). m1A modification impairs base pairing of tRNA-anticodons with the mRNA initiation codon, inhibiting translation initiation (**9**). Both A-to-I editing and pseudouridine modification alter start or stop codons of mRNAs, blocking mRNA transport/translation (**10**, **11**, **12**).

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