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REVIEW

The emerging role of mRNA methylation in normal and pathological behavior

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Covalent RNA modifications were recently rediscovered as abundant RNA chemical tags. Similarly to DNA epigenetic modifications, they have been proposed as essential regulators of gene expression. Here we focus on 3 of the most abundant adenosine methylations: N6-methyladenosine (m^6A), N6,2′-O-dimethyladenosine (m^6Am) and N1-methyladenosine (m^1A). We review the potential role of these modifications on mature mRNA in regulating gene expression within the adult brain, nervous system function and normal and pathological behavior.

Dynamic mRNA modifications, summarized as the epitranscriptome, regulate transcript maturation, translation and decay, and thus crucially determine gene expression beyond primary transcription regulation. However, the extent of this regulation in the healthy and maladapted adult brain is poorly understood. Analyzing this novel layer of gene expression control in addition to epigenetics and posttranslational regulation of proteins will be highly relevant for understanding the molecular underpinnings of behavior and psychiatric disorders.

KEYWORDS

behavior, m^1A, m^6A, m^6Am, post-transcriptional regulation, psychiatric disease, RNA modification

1 | INTRODUCTION

The brain is a unique and complex structure that consists of a large number of highly specialized, majorly post-mitotic cells. These cells work together in a highly-synchronized fashion to execute complex activity and regulation via molecular, cellular and circuit-associated mechanisms. Together, the symphony of coordinated cells encodes a variety of brain functions ranging from homeostasis and support functions to complex behavior. Since all brain cells essentially share the same genomic information, all functional specialization and response to external stimuli, including short- and long-term systems adaptation, is achieved via gene expression regulation. Therefore, understanding all layers of gene expression regulation is critical in understanding this highly complex system both during brain development and in the postnatal brain.

Regulation of gene expression involves primary transcription regulation by transcription factors. Additionally, several epigenetic mechanisms are involved in short- and long-term adaptation of gene expression to challenges. These mechanisms include DNA methylation, chromatin and histone modifications, non-coding RNAs (ncRNAs) and posttranslational regulation of proteins. It has recently been rediscovered that, similarly to the epigenetic code on DNA, RNA as the functional mediator of gene expression undergoes substantial regulation by a diverse layer of covalent modifications. These RNA modifications, collectively termed the epitranscriptome, can profoundly influence RNA maturation, stability, location, and availability to protein translation, and thus determine gene expression beyond simply regulating RNA abundance. Therefore, this introduces yet another layer of potentially regulated and stimulus-adaptive gene expression control.

Detailed analysis of the epitranscriptome has only recently begun but impressive progress has already been made. This is primarily due to advances in the research tools available, which also made epitranscriptome analysis the "Method of the Year"[1] (Nature Methods Editorial, 2017). Here, we attempt to give an introduction to this exciting yet incipient area of research and integrate it into the conceptual

framework of gene expression regulation in the adult brain. Furthermore, we seek to explore its putative role in normal and pathological behavior. However, as a result of the relative young age of this field, there are still many gaps in the data waiting to be filled soon.

2 | THE EPITRANSCRIPTOME

There are over 100 known covalent base modifications found on almost all types of RNA including mRNA, tRNA, rRNA and snRNA.[2] These modifications are being collected in large databases such as MODOMICs, which currently holds 144 modifications together with relevant information on pathways and references[3] (http://modomics.genesilico.pl) and RMBase, which has collected thousands of modification-sites from over 100 different modifications identified by high-throughput sequencing[4] (http://mirlab.sysu.edu.cn/rmbase/). The majority of these modifications were originally discovered in the 1960s and 1970s but, due to technical limitations, attracted little attention in their potential to regulate gene expression post-transcriptionally.[5,6] The most abundant modifications on protein-coding mature mRNAs in the brain, and the focus of this review, are methylations on adenosine (including N6-methyladenosine, m^6A; N6,2′-O-dimethyladenosine, m^6Am; and N1-methyladenosine, m^1A) (Figure 1). The brain also harbors several other modifications[125], for example, pseudouridine Ψ,[7–9] 5-methylcytosine m^5C[10,11] and A-to-I editing.[12,13] However, most of these are more abundant in rRNAs and tRNAs than in mRNAs. Finally, mRNA molecules can be further modified on a whole molecule level by 5′ mRNA capping and polyadenylation, which facilitate transcript stability, nuclear export, translation initiation and dynamic changes of secondary structure of RNA.[14,15] Although we focus here on mature mRNAs, it should be noted that introns in unspliced pre-mRNA (hnRNA[9,16–19]) and small and long non-coding mRNA are also widely methylated.[20–22]

3 | mRNA ADENOSINE METHYLATION

m^6A is the most abundant internal modification first described in 1974.[23–27] m^6A is also the most extensively characterized internal modification in mammalian mRNA[16,28] owing to the power of next-generation sequencing, which was widely adapted for this modification first. Currently, RMBase contains over 62 000 m^6A peaks in over 10 000 genes for the mouse and over 118 000 m^6A peaks in over 12 000 genes for the human transcriptome (Reference [4]; data set as of 20-10-2015). The m^6A modification is typically located in a consensus motif (DRACH/GGAC), although a considerable amount of m^6A sites does not locate to these core motifs (eg, 23 to 31% for the DRACH motif,[29]). m^6A is enriched near stop codons and in 5′ untranslated regions (UTRs), as well as to a lesser extent in introns and long internal exons.[16,28–30] Watson-Crick pairing with U is not disturbed but may modulate secondary structure thus predisposing

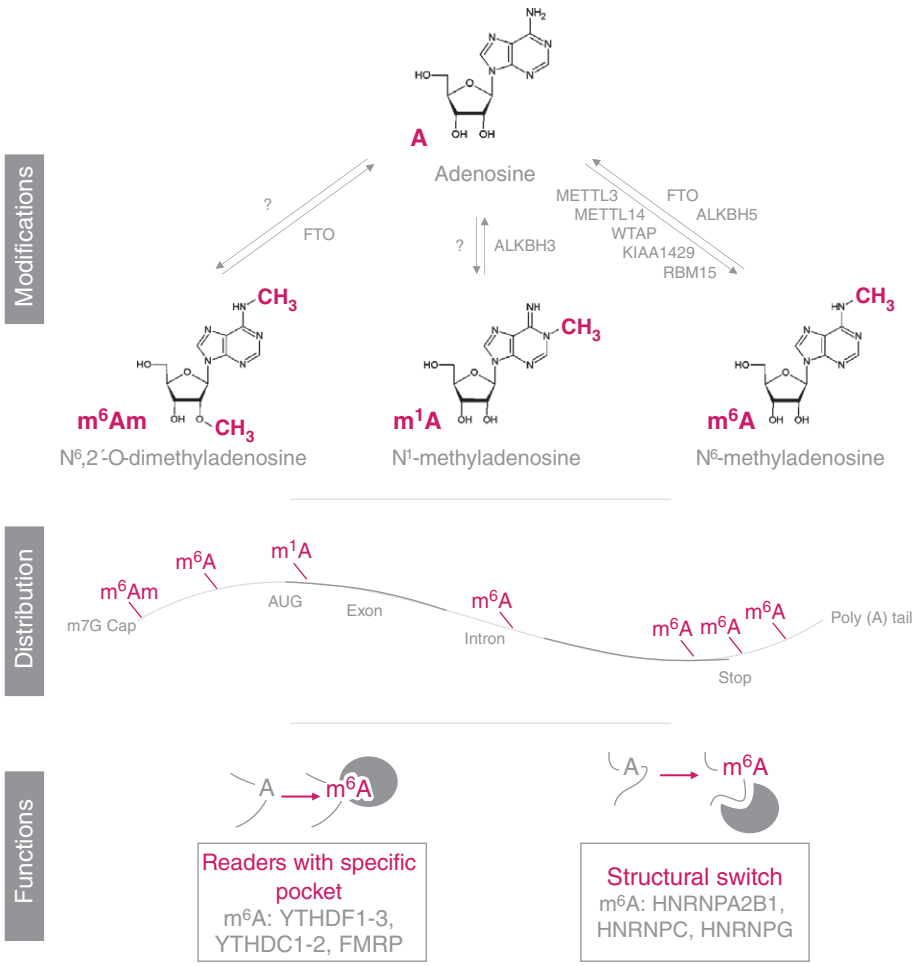

FIGURE 1 RNA adenosine methylation marks on mRNAs in the brain. The adenosine methylations m^6A, m^6Am and m^1A are the most abundant modifications on mature mRNAs in the brain. Several methyltransferases and demethylases for them have been discovered, enabling them to be highly dynamic marks. They appear on characteristic positions within transcripts and may function among others via binding of specific readers or via alterations of RNA structure

the respective RNA region for recognition by binder proteins.[14,18,31,32]

Several highly conserved m^{6}A-metabolizing enzymes have been discovered, accentuating this modification as a prime candidate for dynamic regulation (Figure 1). These include a methyltransferase complex with both catalytic and regulatory units including METTL3, METTL14, WTAP, KIAA1429 and RBM15/B,[27,30,33–35] with METTL3 shown to be the main methyltransferase.[36–38] For removal of m^{6}A, there are at least 2 demethylases, Fat Mass and Obesity-Associated (FTO) and Alkylated DNA repair protein alkB homolog 5 (ALKBH5).[39–41] The existence of this writer and eraser network is widely thought to signify that m^{6}A methylation on a given transcript is highly dynamic and readily reversible. However, more recent reports indicate that m^{6}A is mainly deposited co-transcriptionally on nascent RNA that is still associated with chromatin[17,42] and thus argue that once RNA is released from chromatin, the modifications are surprisingly static.[17,43] While this does not prevent m^{6}A from being regulated in a highly dynamic fashion, it may limit the spatial and time-window of dynamic m^{6}A regulation to the newly produced transcripts and emphasizes the importance of regulation of tagged transcripts by mRNA stability. The cellular consequences of m^{6}A modification depend on its specific site within the target transcript and the binding of additional m^{6}A-reader proteins. Among m^{6}A-reader proteins are nuclear and cytoplasmic proteins of the YT521-B homology (YTH)-domain-family (YTHDF1, YTHDF2, YTHDF3, YTHDC1 and YTHDC2) and HNRNP-proteins (HNRNPA2B1, HNRNPC and HNRNPG).[5,6,44,45] A recent interactome study of m^{6}A identified further binding partners including the neuronal RNA-binding and translation-regulating proteins FMR1, FXR1 and FXR2.[46] Cellular functions of m^{6}A include regulation of RNA maturation as alternative polyadenylation,[47] splicing[18,48,49] and nuclear export. However, the actual extent of splicing regulation by m^{6}A is still unclear.[17]

The main function of m^{6}A seems to be in regulating and distributing transcripts into either RNA decay[50,51] or translation pathways including both promotion and inhibition of translation.[50,52–54] So far it is largely unclear how specificity of the different enzymes and readers to single transcripts and target sites is achieved. Interestingly, m^{6}A on non-mRNA/rRNA/tRNA-species has similar functions, including the control of miRNA biogenesis by m^{6}A on pre- and pri-miRNAs,[48,55] regulation of translation by m^{6}A in circular RNAs[56] and changes of conformation by m^{6}A in long ncRNAs.[57]

Regarding cellular functions, m^{6}A was found to control a plethora of systems, among others stem cell proliferation and differentiation,[58–61] cellular heat-shock response,[54] spermatogonial differentiation,[62] maternal-to-zygotic transition,[5,6] X-chromosome inactivation,[34] UV DNA damage response[63] and tumorigenesis.[64]

A chemically closely related modification, m^{6}Am, is a 2′-O-methylated base found at the second nucleotide of certain mRNAs as well as snoRNAs, thus at the first nucleotide following the m^{7}G cap[29,30,40,65] (Figure 1). m^{6}Am is co-detected by the most commonly used anti-m^{6}A antibody, making currently available m^{6}A-data potentially a mixture of both m^{6}A and m^{6}Am.[29,40] m^{6}Am rather than m^{6}A is the preferred substrate of the demethylase FTO *in vitro*,[40] although cellular action *in vivo* may be different due to the higher stoichiometry of m^{6}A compared to m^{6}Am. The m^{6}Am methyltransferase and potential further demethylases are not known yet. m^{6}Am stabilizes mRNA by preventing DCP2-mediated decapping and mRNA decay, which is potentially mediated by miRNAs.[40]

Lastly, m^{1}A is a dynamic modification recently reported to be added on transcripts of over 4000 genes[66,67] at an average methylation level of 20%.[66] These sites were enriched around the start codon upstream of the first splice site, around the translation initiation sites (Figure 1,[66–68]). m^{1}A, like m^{6}A and m^{6}Am, is a dynamic modification and can be removed by ALKBH3.[66,67] The methyltransferases catalyzing m^{1}A on mRNA are yet to be fully identified (Figure 1) although several enzymes have been reported for rRNA and tRNA including ALKB, ALBH1, TRM6, TRM10 and TRM61.[69–71] In contrast to m^{6}A and m^{6}Am, m^{1}A disturbs the Watson-Crick base pairing and thus likely alters protein-RNA interactions and RNA secondary structures through electrostatic effects. It further may affect translation by facilitating non-canonical binding of the exon-exon junction complex at 5′ UTRs devoid of 5′ proximal introns.[68]

Finally, m^{6}A and m^{1}A as well as potentially m^{6}Am marks are highly conserved between mouse, primate and human transcriptomes,[16,66,72] strongly indicating an evolutionary conserved mechanism of RNA regulation.

4 | mRNA METHYLATION IN THE BRAIN

Brain m^{6}A mRNA methylation is comparably high and increases during development.[28] The abundance of other adenosine methylations during development still needs to be assessed. A recent report showed m^{6}A to be critical for perinatal and early postnatal cortical neurogenesis in mouse brain and in human induced pluripotent stem cell (iPSC) derived organoids with depletion of *Mettl14* or *Mettl3* leading to a protraction of neurogenesis via prolonging the cell-cycle of radial glia cells.[73] This may be mediated by m^{6}A-dependent decay of transcripts typical for late progenitor cells and differentiated neurons in neural stem cells.[73] Comparing human and murine fetal m^{6}A-epitranscriptomes, the authors further concluded that m^{6}A mRNA methylation in the developing human brain is as well more prevalent as enriched for genes related to mental disorders.[73]

Switching focus to the adult brain, it is unique in its multitude of specialized brain regions and cell types. m^{6}A RNA methylation levels and patterns were shown to be highly diverse in different brain regions, using the example of mouse cerebellum and cerebral cortex.[74] Furthermore, single-cell RNA-Seq data has shown that all known m^{6}A enzymes and readers are expressed in all major brain cell types including neurons and glia and their subtypes (eg, Reference 75). The FTO protein is also expressed in non-neuronal cell types.[76,77] Cell-type specific abundance of the modifications, as well as other RNA methylation enzymes and readers, still needs to be investigated.

Within a given cell-type, different m^{6}A enzymes and binding proteins may potentially possess distinct regional and subcellular distributions. This is likely significant in neurons due to their high cellular compartmentalization, requiring specific mechanisms for long-distance distribution of mRNAs and proteins across axons and dendrites. Paired with local translation at neuronal synapses,[78] this provides yet another mechanism for the temporal and spatial

regulation of gene expression specific to the brain. Interestingly, fragile X mental retardation protein (FMRP), a neuronal RNA-binding protein that forms RNA transport granules regulating dendritic localization of RNAs as well as inhibits transcript translation including local synaptic translation,[79,80] was recently identified as a RNA-sequence-context-dependent reader for m^{6}A.[46] Furthermore, it was proposed that FTO protein in cells *in vitro* and in neurons *in vivo* may shuttle between and be located in both the nucleus, cell body and dendrites including synapses, enabling local RNA methylation dynamics.[77,81] Similar mechanisms of local synaptic action at the synapse have been proposed for RNA m^{5}C methylation.[82] In contrast, writer and eraser enzymes of RNA methylations are generally considered and demonstrated by several studies to be strictly nuclear proteins. Even more, the addition and removal of m^{6}A was proposed to be limited to chromatin-associated mRNAs before they are exported into the cytoplasm.[17] Therefore, the distribution of methylation enzymes and reader proteins in neurons and especially in synaptic compartments still needs to be extensively tested. If proved, it would enable additional local regulation of transcript translation and decay crucial for such highly compartmentalized cells. Finally, m^{6}A enzymes and reader expression may be dynamically regulated within different brain regions as shown for example for FTO[83,84] enabling region-specific control of RNA methylation.

5 | mRNA METHYLATION IN NORMAL AND PATHOLOGIC BEHAVIOR

Here, we focus on the role of mRNA adenosine methylation in the regulation of emotional and cognitive behaviors. Gene-specific quantitative regulation of RNA methylation may underlie gene expression regulation in the brain and thus the encoding of normal and maladaptive behavior (Figure 2). On a cellular level, dynamic changes of m^{6}A and m^{1}A have been observed in cell-systems in response to heat-shock and starvation stress.[54,66] It is mostly unknown to what extent brain m^{6}A is controlled by external stimuli *in vivo* with the exception of m^{6}A reported to be regulated during memory formation.[77,85] m^{6}A was further implicated in regulation of dopaminergic brain networks and the expression of cocaine response, implying a potential role in the reward system.[86] Additionally, gene expression changes of adenosine methylation enzymes have been described in mice subjected to learning tasks with fear memory increased after knock-down of FTO in prefrontal cortex or in the dorsal hippocampus,[77,85] suggesting a role for m^{6}A/m^{6}Am in experience-dependent plasticity.[87] Based on loss-of-function animal models, m^{6}A modification was proposed to be essential for early development given the embryonic lethality of germline knockout mice for *Mettl3*[60] and *Wtap*.[88] Furthermore, mice with *Mettl14* knockout in the developing mouse brain die before reaching adulthood.[73] Similarly, the m^{5}C methyltransferase *Nsun2* is critical for differentiation of human neural stem cells and mouse early brain development.[89] In contrast, increasing m^{6}A by knockout of the demethylase enzymes (*Fto* and *Alkbh5*) produces mainly metabolic phenotypes; including postnatal growth retardation, increased energy expenditure, altered locomotor activity and altered neuronal response to food cues in *Fto* knockout mice[86,90,91] and impaired fertility in *Alkbh5* knockout mice.[41] Importantly, homozygous *Fto* knockout mice also have increased postnatal death rates potentially as a consequence of their metabolic phenotypes.[90]

Furthermore, a variant in an intron within the human FTO gene is associated with obesity.[92,93] Whereas this association has been confirmed across several studies including different populations and age groups, the phenotype is likely not mediated through the FTO gene that the single-nucleotide polymorphism (SNP) was mapped to, but rather through long-range regulation to the neighboring genes IRX3 and IRX5.[94–96] This may also explain the contradictory findings of different metabolic effects in *Fto* knockout mice.

Finally, the role of m^{6}A-reader proteins in the brain so far is unknown apart from one study that suggests the m^{6}A-reader YT521-B regulates neuronal function in drosophila, with motoric and behavioral defects seen in knockout flies.[97]

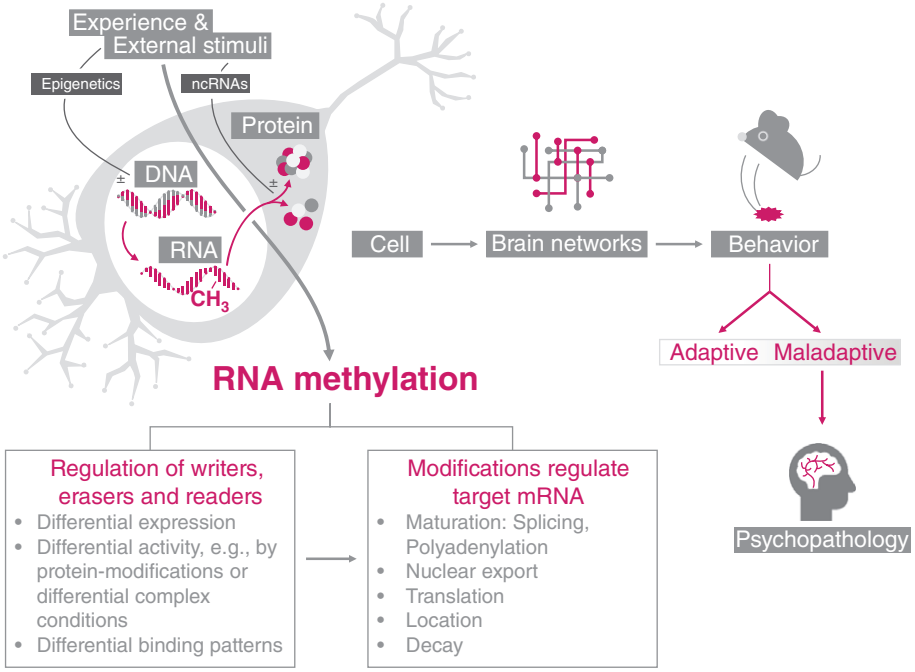

FIGURE 2 Mechanisms by which RNA methylations may regulate gene expression in response to external stimuli, behavior and psychiatric diseases. External stimuli and experience may dynamically alter RNA methylation enzymes and reader proteins as well as modifications on specific transcripts. This may regulate gene expression of transcripts crucial for cellular function and neuronal activity, ultimately contributing to adaptive or maladaptive behavior. As fine-tuning of transcriptional and translation is central to normal human brain function, regulation of RNA methylation thus may also be important for psychiatric disorders

Taken together, emerging evidence indicates that RNA methylation may be crucial for transcript fate and the subsequent protein levels in neurons and other cells of the brain, thus essential for brain function and plasticity and enabling appropriate adaptation to external challenges (Figure 2). However, the exact molecular and cellular mechanisms that govern this regulation still need to be identified. Since dysregulation of epitranscriptomic mechanisms may lead to maladaptive behavior, future studies should address this aspect.

6 | mRNA METHYLATION IN HUMAN BRAIN PATHOPHYSIOLOGY

Gene polymorphisms have long been investigated for their contribution to stress and resiliency as well as genetic risk factors for psychiatric disorders.[98] Several variants in RNA methylation enzymes were associated with risk for psychiatric disorders in small cohorts. Variants include human FTO[99–103] and ALKBH5[104] as well as associations to many non-psychiatric disorders including obesity and cancer survival.[93,105–108]

Likewise, RNA methylations may be involved in the disease pathology of psychiatric diseases beyond gene polymorphisms. Indeed, psychiatric disorders largely deviate from the "common disease, common variant" hypothesis suggesting the need for additional regulating systems. Increasing evidence suggests that fine-tuning of transcriptional regulation by gene-environment interactions is central to the etiology of psychiatric disorders. Evidence includes disease-associated SNPs in enhancer regions,[98] epigenetic changes[109] such as chromatin conformation[110] and histone modifications[111] as well as short and long ncRNAs.[112,113] Therefore, elucidating the role of mRNA methylation in regulating normal and aberrant neuronal activity and brain functions may add to a better understanding of psychiatric disorders (Figure 2). mRNA methylation may represent a particularly interesting mechanism to target for treatment as it could fine-regulate or even counteract gene expression regulation caused by other gene-environment interaction mechanisms, for example pathologically maladapted regulation patterns inflicted by trauma.

7 | FUTURE CHALLENGES

Epitranscriptomic modifications are emerging as a widely-underestimated part of the molecular regulation of the adult brain. We are only starting to understand the extent and complexity of both the regulation and importance of mRNA methylation *in vivo*. To date, several RNA modifications have been mapped in a transcriptome-wide fashion in baseline cells, including comprehensive maps of m^{6}A in unstimulated mouse brain[28,86] and several writer-, eraser- and reader-proteins have been described. Most modifications seem to be crucial in stem cells and during organism development[60,114] but it is mostly unclear how dynamic the different modifications are in an intact post-mitotic *in vivo* system like the adult brain. Precise quantification of modification dynamics in the brain will be crucial to elucidate the importance of these mechanisms for brain function. Currently, methods to precisely quantify regulation of RNA methylation beyond qualitative detection require large amounts of input material or are limited to global or low-throughput gene- and site-specific measurements (please refer to a recent comprehensive review of techniques by References 115). SCARLET, a ligation-based method, provides quantification at single-base resolution but in a low-throughput manner.[116,117] Most other site-specific detection methods rely on antibodies with potential cross-reactivity to different modifications and yet unclear quantitative nature.[29,66] Protocols for identifying the precise location of m^{6}A RNA methylation at single base resolution have only very recently become available, including photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) and high-throughput sequencing of RNA isolated by crosslinking and immunoprecipitation (HITS-CLIP).[29,47,118] Given the enormous cellular heterogeneity of the brain, assessing RNA modification dynamics in a cell-type-specific manner will be important.

Furthermore, future work needs to identify the upstream regulator cascades of methylation *in vivo* as well as downstream consequences per specific methylation event, including mapping of cell-type-specific binding by reader-proteins and molecular consequences of such binding. To this goal, it will also be important to integrate investigations of mRNA methylation patterns with measurements of RNA abundance, alternative polyadenylation, alternative splicing, translation efficiency and protein expression.

Genetic and pharmacological tools to investigate consequences of single modifications at certain genes *in vitro* and *in vivo* are still in their infancy. Conditional knockout animals for most of the m^{6}A enzyme and reader proteins recently became available allowing for diverse examination of cellular and behavioral consequences of manipulation of m^{6}A in specific (brain) cell types by deletion of single key players or whole functional families. Unfortunately, the present lack of tools to manipulate specific single-site modifications *in vivo* in a temporal and cell-type-specific manner still limits the causal investigation of cellular consequences of covalent RNA manipulations.

Several clustered regularly interspaced short palindromic repeats (CRISPR) approaches have been recently described that direct interference complexes toward single-stranded RNAs and are potentially useful for visualizing, degrading and binding mRNAs, including the bacterial RNase C2c2, RCas9 and Cas13a.[119–122] These upcoming CRISPR/Cas9 technology derived systems may soon be available not only to target mRNAs directly but also to carry RNA-modifying enzymes to specific targets.[123]

Taken together, recent methodological developments will allow the assessment of not only the precise dynamics of RNA modifications *in vivo* but also their role in regulating normal and pathological behaviors. How RNA modifications differ by sex and age as well as their contribution to individual differences related to resiliency or susceptibility to environmental challenges and vulnerability to psychiatric disorders would provide some much-needed insight.

8 | OUTLOOK

Although RNA modifications have been known for many decades, only recent work has revealed their actual abundance and function in mRNAs. Elucidating the underlying molecular and cellular processes that regulate the fine-tuning of transcription- and translation-control

in the developing and adult brain is essential for understanding normal and pathological behavior and, ultimately, psychiatric disorders. RNA modifications represent a pivotal layer of regulation of gene expression previously under-appreciated. The nature of RNA modifications enables them to regulate gene expression beyond the regulation of mRNA abundance itself and thus are inclined to be a crucial fine-tuner of protein levels once RNA becomes available in a cell. This level of regulation should also be kept in mind when estimating protein expression using transcriptomic data.[124] Integrating measurements of RNA modifications with those of DNA modifications as well as posttranslational protein regulation will be critical for understanding the complex molecular underpinnings of normal and pathological behavior.

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