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Epitranscriptomic Remodeling of N6-Methyladenosine (m6A) RNA Marks in CRISPR-Edited Genomes: Emerging Implications for Off-Target Genetic Instability and Precision Gene Therapy

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Abstract

With the advent of epitranscriptomics, there is the addition of a regulatory layer of control over gene expression which goes beyond DNA sequence and chromatin-based regulation and encompasses dynamic chemical RNA modification. Of these N6-methyladenosine (m6A) is the most common interior modification of eukaryotic messenger RNA (mRNA) and is crucial in maintaining RNA stability, splicing, nuclear export, and translational efficiency. M6A deposition, removal and functional interpretation are regulated by an extensive system of methyltransferases (writers), demethylases (erasers) and RNA-binding proteins (readers), which allow a rapid and reversible regulation of gene expression in response to cellular signals.

Simultaneously, the emergence of CRISPR-Cas genome editing technologies has transformed the field of molecular biology and provided a new opportunity in the field of precision gene therapy. Although significant focus has been placed on the conceptualization of off-target DNA mutation and genomic instability, the consequences of genome editing on RNA layers

of control, and especially, the epitranscriptomic changes have not been fully investigated. Recent data indicate that, following the formation of CRISPR-induced DNA double-strand breaks and the ensuing activation of DNA damage response pathways, the global state of cells can be changed, with a potential impact on m6A deposition patterns, including: chromatin remodeling, transcriptional reprogramming, and stress signaling.

This review offers the highest possible idea of the m6A epitranscriptomic environment and its regulatory apparatus, and then a deeper discussion of CRISPR-Cas systems and the cellular reactions related to it. We make the mechanistic case of the interaction between genome editing and m6A remodelling, and how the transcriptional dynamics and RNA-binding protein activity perturbation can cause transcriptome-wide changes in m6A distribution. We also compare the existing methods of m6A modifications detection, their advantages, and shortcomings, and address their possibilities of use in CRISPR-based research.

Notably, we discuss the consequences of the CRISPR-based epitranscriptomic variability to precise gene therapy, in which unintended RNA-level regulatory alterations can influence treatment safety, efficacy and reproducibility. Combining the findings of RNA biology, genome engineering, and high-throughput sequencing technologies, this review highlights the importance of taking into consideration epitranscriptomic measurements in genome editing models. The interaction between the CRISPR systems and m6A regulation will need a better insight, as it will be the key to more precise and safer therapeutic approaches.

Keywords: Epitranscriptomics; N6-methyladenosine (m6A); CRISPR-Cas9; Genome Editing; RNA Modification; Off-target Effects; DNA Damage Response; Precision Gene Therapy.

1. Introduction

Over the last few years the central dogma of molecular biology has grown beyond the linear expression of genetic information between DNA and RNA to protein, and many levels of regulatory complexity fine tuning gene expression have been added. Epigenetics is one of these regulatory tiers, and it has been known since ancient times to regulate the chromatin structure and transcription without changing the underlying sequence (1,2,3). Nevertheless, an emerging fast changing area epitranscriptomics has added another layer of post-transcriptional regulation, in which chemical modifications of RNA molecules dynamically affect their fate and function. Of the more than 170 known RNA modifications, the most common and functionally relevant internal modification of eukaryotic messenger RNA (mRNA) has been N6-methyladenosine (m6A), which is essential in the stability of RNA, alternative splicing, nuclear export and translational efficiency (4,5,6).

The deposition of m6A and removal are controlled by a carefully coordinated group of methyltransferases (also known as writers), demethylases (also known as erasers), and RNA-binding proteins (also known as readers), allowing the fast and reversible regulation of gene expression in response to developmental signals and environmental conditions. It is this dynamism that renders m6A a significant regulatory molecule in numerous biological processes, i.e., cell differentiation, stress responses, and disease pathogenesis (7,8,9). It is worth noting that m6A dysregulation has been associated with a wide range of pathological diseases, such as cancer, neurodegeneration, and immune disorders, which makes its biological and clinical relevance hard to overlook (10,11,12).

At the same time, the introduction of CRISPR-Cas genome editing technologies has completely transformed the world of molecular biology, which has guaranteed more accuracy and effectiveness in targeted manipulation of genes. Particularly, the CRISPR-Cas9 system has found extensive use in functional genomics, as well as in therapeutic-gene correction. Although this has the potential to transform, there is the issue of unintended consequences particularly off-target DNA mutation and genomic instability, which is a significant hindrance in its clinical translation. Although the literature has been much on the characterization of DNA-level off-target effects, limited studies have been done on the possible effects of genome editing on RNA regulatory layers, and epitranscriptomic modifications in particular (13,14,15).

There are new indications that CRISPR-mediated genome editing can cause more profound cellular perturbations than changes in the DNA sequence. These consist of the stimulation of DNA damage response pathways, chromatin remodeling, transcriptional program shifts all of which can indirectly affect the epitranscriptomic landscape. Since m6A deposition is sensitive to transcriptional dynamics and cellular stress cues, it is likely that genome editing actions may cause massive remodelling of m6A patterns, in turn influencing RNA metabolism and downstream gene expression networks (16,17,18).

In this respect, it is of paramount importance to learn about the interaction between CRISPR-induced genomic perturbations and m6A-mediated epitranscriptomic regulation. These interactions could carry far-reaching consequences on cellular homeostasis, phenotypic homeostasis, and the safety of gene-editing based

therapeutic approaches (19,20,21). The current review seeks to review the existing literature in the crossroads of genome engineering and epitranscriptomics to reflect new mechanisms by which CRISPR editing can have an impact on m6A dynamics. In addition, it aims at determining some of the knowledge gaps and suggest future research directions to improve how unintended regulatory consequences are evaluated and mitigated in an effort to further develop safer and more precise gene therapy strategies (22,23,24).

2. The Epitranscriptomic Landscape of m6A RNA Modification

N6-methyladenosine (m6A) is the most common internal modification in eukaryotic messenger RNA (mRNA), and it is an essential part of epitranscriptomic regulatory network (25,26,27). The process is the methylation at nitrogen-6 of adenosine residues, and is largely overrepresented in consensus elements in the form of DRACH motifs (D = A/G/U, R = A/G, H = A/C/U). Transcriptome wide mapping analyses have shown that m6A sites are not randomly distributed, and are very much enriched in 3 end regions (3' UTR), near stop codons, and in long internal splicing and these findings indicate a very strict pattern of deposition that may have a function of great importance (28,29,30).

RNA m6A is a functional regulator of RNA metabolism, with many roles in the mRNA life cycle. It regulates the stability of mRNAs by regulating their decay or lengthening their half-life based on the reader proteins that it interacts with. Also, M6a can also be important in control of the efficiency of translation, and it frequently promotes the quick production of proteins under cellular stress conditions. It also plays roles in making alternative splicing choices, nuclear export, and localization of RNA thus combining transcriptional products with post-transcriptional control systems (31,32,33).

Dynamicity and reversibility is one of the properties of m6A modification. Unlike the fixed genetic mutations, the m6A marks can be erected and erased promptly depending on the cellular conditions and thus the cells can be adapted to the extended environmental conditions. The plasticity is important in embryonic development, stress adaptation and stem cell differentiation (34,35,36).

It is worth noting that cellular stressors such as oxidative stress, heat shock, and DNA damage have been demonstrated to cause significant changes in m6A patterns of distribution, indicating that it is a responsive regulatory layer (37,38,39).

The m6A epitranscriptomic landscape is very sensitive to transcriptional activity and cellular signaling pathways, therefore it is highly prone to perturbations created by external interventions, such as genome editing technologies. The key to comprehending how CRISPR-mediated genomic changes can indirectly remodel the RNA regulatory networks is therefore in having a basic understanding of the underlying properties and functional implications of m6A (40).

Table 1. Key Features and Functional Roles of m6A RNA Modification (41,42,43).

Feature	Description	Biological Significance
Chemical Nature	Methylation at the N6 position of adenosine	Most abundant internal mRNA modification
Consensus Motif	DRACH sequence (e.g., RRACH)	Determines site-specific deposition
Transcript Distribution	Enriched near stop codons, 3′ UTRs, and long exons	Indicates regulatory hotspots
Reversibility	Dynamically added and removed	Enables rapid cellular adaptation
Role in mRNA Stability	Can promote decay or stabilization depending on reader proteins	Controls transcript lifespan
Impact on Translation	Enhances or regulates translation efficiency	Supports rapid protein synthesis
Role in Splicing	Influences alternative splicing events	Contributes to transcript diversity
Response to Stress	Altered under stress conditions (e.g., DNA damage,	Links
Biological Processes	Development, differentiation, immune response	Essential for cellular function and homeostasis

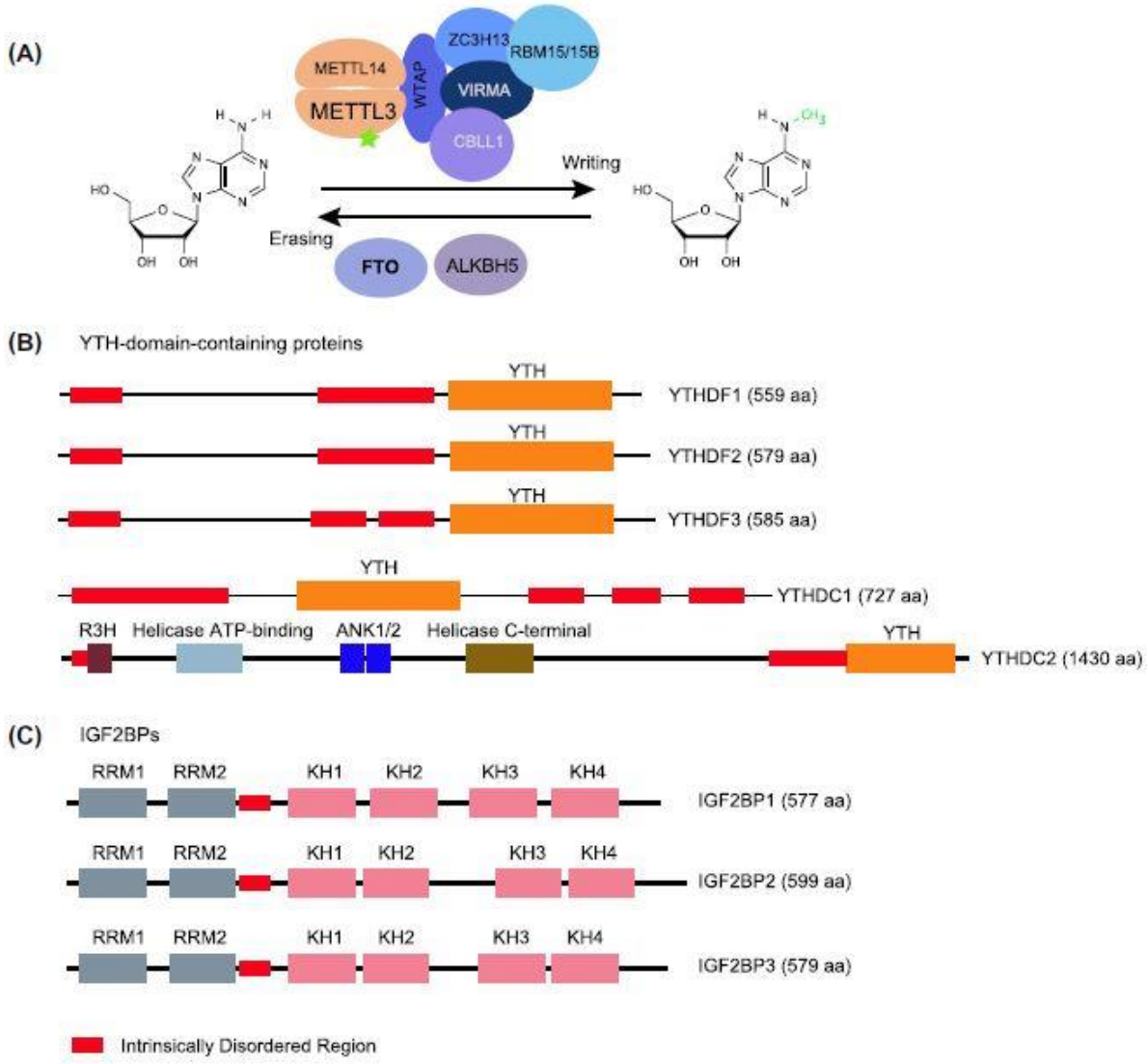

Figure 1. *m6A writers, readers, and erasers. (A) The RNA modification m6A is deposited by a methyltransferase complex comprising a heterodimeric core consisting of METTL3 and METTL14, along with additional accessory subunits including WTAP, VIRMA, ZC3H13, CBLL1, and RBM15/15B. METTL3 functions as the only catalytic subunit, converting adenosine (A) to N6-methyladenosine (m6A). Below, two m6A erasers, FTO and ALKBH5, are illustrated. (B) The domain architecture of canonical m6A readers, YTH-domain-containing proteins (YTHDF1/2/3 and YTHDC1/2) which directly recognise m6A through their YTH domain. The protein sizes shown on the right are in accordance with annotations in the human genome. Note: recent evidence suggests that YTHDC2 may bind to RNA independently of m6A [82], contrasting with the original finding [83]. (C) The domain architecture of non-canonical m6A readers IGF2BP proteins (IGF2BP1/2/3) which recognise m6A through their KH domain. The protein sizes shown on the right are in accordance with annotations in the human genome.*

3. Molecular Machinery Regulating m6A (Writers, Erasers, and Readers)

A highly coordinated and dynamic regulatory network of three major classes of proteins namely writers, erasers and readers controls the functional role of N6-methyladenosine (m6A) modification. All these factors are known to control deposition, removal and interpretation of m6A tags, which in turn provides the coordination of post-transcriptional regulation of genes with extraordinary precision (44,45,46).

The installers in the installation process of m6A on RNA molecules are the methyltransferase complexes known as the writers. The key constituents of this complex are the METTL3, which is the catalytic subunit, and METTL14 which is an RNA-binding scaffold. Other such proteins that regulate substrate specificity, localization and efficiency of methylation incorporate other regulatory proteins such as WTAP, VIRMA (KIAA1429) and RBM15. The latter multi-protein complex ensures that the m6A deposition is context-dependent and site-selective and typically linked with transcriptional activity (47,48).

In contrast, the erasers are demethylases that remove m6A posts to underline the reversible nature of the epitranscriptomic mark. Two of the key identified demethylases are FTO and ALKBH5 all of them are members of the AlkB family of dioxins. These enzymes enable dynamically reprogramming of RNA methylation patterns in response to physiological and environmental signals, including cellular stress and metabolic reaction (49).

The final action is the functional result of the m6A marks that are mediated by a pool of assorted RNA-binding proteins referred to as readers that selectively binds methylated transcripts. Nuclear readers Nuclear readers, such as YTHDC1, take part in the core action of controlling the destiny of the m6A-modified RNA. Fate determination is also dependent on members of the YTH domain family which include YTHDF1, YTHDF2 and YTHDF3. Depending on the reader to which the m6A is conjugated, the mRNA can either be destroyed, translated, or regulated to be spliced and exported (50,51).

It is these interactions and relationships between writers, erasers and readers that give rise to cellular homeostasis. This regulatory network is susceptible to perturbation that causes the mass change in the expression of genes to become important in both normal physiology and disease states (52,53).

4. CRISPR-Cas Systems and Genome Editing-Induced Cellular Responses

Genome engineering has changed with CRISPR-Cas systems due to the possibility of exact, efficient and programmable manipulation of DNA sequences. The best known of them is CRISPR-Cas9 platform which uses a guide RNA (gRNA) to direct the Cas9 endonuclease to a specific locus in the genome where it causes a double-strand break (DSB). This targeted cleavage may trigger endogenous repair signaling, composed of most parts of non-homologous end joining (NHEJ) and homology-directed repair (HDR), which is the ultimate character of the editing outcome (54,55).

Although the CRISPR technology provides unmatched manipulation of the genetic aspect, the DSB induction is a severe cellular stressor. DNA damage resulting in activation of DNA damage response (DDR) pathways causes a series of molecular events that involve recruitment of repair factors, chromatin remodeling, and transient cell cycle arrest. These reactions are necessary to sustain genome integrity but can also have unintended effects especially when the error-prone repair mechanisms are involved (56).

In addition to direct changes in DNA, the editing via CRISPR has been demonstrated to induce an effect on the general cellular processes. As an example, formation of DSBs may result in the alteration of chromatin accessibility, and consequently transcriptional activity of the target and non-target loci. Also, genome editing can cause oxidative stress and inflammatory signaling pathway changes, which further promote global changes in the profile of gene expression (57).

Notably, these cell responses are not confined to the DNA level but may be extended to the RNA regulation systems. Various modifications in transcription and chromatin organization can have an indirect effect on RNA processing and alteration, such as epitranscriptomic modifications like m6A. Therefore, the CRISPR-induced perturbations can have a cascading effect on not only the genomic stability but also post-transcriptional regulation (58,59).

These inter-relatives help to understand the entire range of CRISPR-related effects, especially in therapeutic situations where accuracy and safety are the most important aspects (60).

5. Interplay Between CRISPR Editing and m6A Epitranscriptomic Remodeling

CRISPR-mediated genome editing and m6A epitranscriptomic regulation is a newly emerging and complicated field of study. Despite the fact that CRISPR-Cas9 is used to target DNA, there is growing evidence that downstream cellular effects of the technology go beyond changes in the genomic context and that it can affect the regulatory landscape of RNA. To be more exact, the activation of DNA damage response (DDR) pathways and the resulting induction of double-strand breaks (DSBs) can provide a cellular environment that facilitates epitranscriptomic remodelling (61,62).

Among the most important processes connecting the CRISPR activity to m6A dynamics is a change in transcriptional programs. RNA polymerase II activity can be modified by DNA damage and chromatin remodelling, and this can control transcription rates and co-transcriptional m6A deposition. Because the

installation of m6A is strictly connected to transcription, any event of disruption to transcriptional kinetics can produce the redistribution of m6A across the transcriptome. In addition, genome editing can trigger stress-responsive signaling pathways, including p53 signaling and oxidative stress response, that have been reported to regulate the expression and activity of m6A regulatory proteins, such as METTL3 and FTO (63,64).

Also, the alterations in chromatin accessibility caused by CRISPR can change the recruitment of RNA-binding proteins and m6A machines to particular genomic loci. It may cause local or global changes in m6A content, which may change the stability of mRNAs, translation, and the cell phenotype. Notably, the effects can be long-term, after the editing event, which brings up long-term transcriptomic instability (65,66).

Other recent research has also suggested that off-target editing events may play an indirect role in the deposition of aberrant m6A, through the disruption of regulatory genes in RNA metabolism. Despite the fact that this area is still in its infancy the existing evidence suggests that epitranscriptomic implications should be taken into account to improve the analysis of CRISPR effects, especially in delicate processes like stem cell editing and gene therapy (67,68).

Table 2. Potential Mechanisms Linking CRISPR Editing to m6A Remodeling (69,70).

CRISPR-Induced Event	Effect on Cellular Processes	Potential Impact on m6A
DNA Double-Strand Breaks (DSBs)	Activation of DDR pathways	Altered m6A deposition via stress signaling
Chromatin Remodeling	Changes in DNA accessibility	Modified recruitment of m6A machinery
Transcriptional Reprogramming	Altered RNA polymerase II activity	Redistribution of m6A across transcripts
Oxidative Stress	Activation of stress-response pathways	Regulation of writers and erasers
Off-target Mutations	Disruption of regulatory genes	Indirect perturbation of RNA modification pathways
Cell Cycle Arrest	Temporary	Changes in RNA processing dynamics

6. Experimental Approaches for Detecting m6A Changes Post-CRISPR Editing

N6-methyladenosine (m6A) modifications can be accurately detected and measured, which is why the study of their impact on the epitranscriptomic environment requires CRISPR-mediated genome editing. Since m6A is dynamic and context-dependent, a multiplicity of experimental and computational strategies has been established to map these modifications with different degrees of resolution, sensitivity and specificity. Nonetheless, research into m6A changes during genome editing poses special technical problems, especially in trying to identify definitive changes caused by editing and background fluctuations (71,55).

One of the most common types of transcriptome-wide m6A mapping using antibody-based enrichment methods include methylated RNA immunoprecipitation sequencing (MeRIP-seq) and m6A-seq. The techniques are based on immunoprecipitation of fragments of RNA that are methylated and then subjected to next-generation sequencing. They offer a general picture of the m6A distribution globally; however, their comparatively low resolution, which usually identifies regions of 100-200 nucleotides, does not allow them to identify the exact site of modification. Besides, the specificity of antibodies and changes in batches can cause experimental bias (72,44).

To address the limitations, techniques with higher resolution have been invented. Single-nucleotide mapping techniques, like miCLIP (m6A individual-nucleotide-resolution crosslinking and immunoprecipitation), allow introducing a mutagenic signature at the m6A sites during reverse transcription. In the same way, methods aided by photo-crosslinking (ex: PA-m6A-seq) enhance specificity by utilizing covalent RNA-protein interactions. Nanopore direct RNA sequencing is a relatively more recent technology that has become a potent antibody-free technology with the ability to identify RNA modifications in real-time at single-molecule resolution. This approach is especially useful when examining changes in epitranscriptomic responses to CRISPR editing, which are subtler, but issues associated with signal noise, base-calling and data interpretation still exist (73,74).

In complement to approaches based on sequencing, liquid chromatography-mass spectrometry (LC-MS/MS) offers very precise quantification of global m6A abundance, but does not include information about location. Thus, it may be required to

combine various orthogonal methods to obtain both quantitative and site-specific information (75,76).

Other factors to consider in CRISPR-edited systems are cellular heterogeneity, editing efficiency and transcriptional responses to stress, each of which can confound interpretation. Matched unedited cells and other controls on appropriate experimental conditions are essential to robust analysis and require advanced bioinformatics pipelines. Finally, these technologies will need further refinement before they can be reliably used to characterize epitranscriptomic changes and what they imply in genome editing (77,78,79).

Table 3. Technologies for m6A Detection and Their Key Features (80,81).

Technique	Principle	Resolution	Advantages	Limitations
MeRIP-seq	Antibody-based enrichment of m6A RNA	Low (~100–200 nt)	Widely used, scalable	Low resolution, antibody bias
m6A-seq	Immunoprecipitation followed by sequencing	Low	Global mapping capability	Limited precision
miCLIP	UV crosslinking induces mutation signatures	High (single-base)	Precise site identification	Technically demanding, complex analysis
PA-m6A-seq	Photo-crosslinking for enhanced specificity	Medium–High	Improved signal-to-noise ratio	Requires specialized protocols
Nanopore Sequencing	Direct RNA sequencing without antibodies	Very high	Single-molecule, real-time detection	Higher error rates, computational challenges
LC-MS/MS	Mass spectrometry-based quantification	No site resolution	Highly accurate global quantification	Lacks positional information

Conclusion

This recent movement toward epitranscriptomics has created a new dimension of important cells that should not be controlled by the DNA sequence or chromatin state but by the dynamic and reversible changes in RNA state. N6-methyladenosine (m6A) is one of them, and has been found to be a key regulatory modification that modulates various processes of RNA metabolism, such as stability, translation, and splicing. Simultaneously, the CRISPR-Cas genome editing technologies have transformed the contemporary molecular biology and have colossal potential in gene correction therapy. Nonetheless, the biological implications of genome editing, as highlighted in this review, go beyond the desired alterations in DNA and can feature numerous, multifaceted regulatory changes.

There is mounting evidence indicating that editing using CRISPR can indirectly reorganize the epitranscriptome by activating DNA damage response and chromatin remodeling and transcriptional reprogramming. Such perturbations of cells have the potential to affect the activity and localization of m6A regulatory machinery, resulting in a change in RNA methylation patterns. Such changes are capable of impacting on gene-expression networks, stable phenotype cells and long-term genomic integrity particularly in sensitive uses such as stem cell engineering and regenerative medicine.

It is interesting to note that CRISPR-related epitranscriptomic variability might also be involved to a further complication in gauging the security and usefulness of accuracy gene therapy. Even though there has been a lot in minimizing the off-target effects at the DNA level, there is a lack of adequate studies at the RNA level to adequately describe the changes in regulation. This amounts to a desperate requirement in the current genome editing evaluation structures, which must be reconciled to ensure the development of truly correct and predictable treatment methods.

It is perceived that the novel high-resolution sequencing schemes, integrative multiple-omics approaches will be instrumental in the disclosing of the entire remodeling of m6A following genome editing. Subsequent studies must consider mapping these changes systematically, determining their functional implications and come up with ways of stemming off these unintended epitranscriptomic effects. Finally, a thorough knowledge of the interaction between CRISPR technologies and RNA modification systems would be necessary to streamline the use of genome

editing and open up their potential as a safe and controlled source of therapeutics.

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