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Viral Immune Escape: The Role of RNA M6a Modifications in Persistent Human Viral Infections and Precision Antiviral Therapy Limitations

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ABSTRACT: Although the use of antiviral drugs has improved, human viral infections are still a serious health problem in the world, as they have the capacity to evade host immunity, to persist and to not be completely eliminated. The methylation of RNA at the N6 position of adenine (N6-methyladenosine or m6A) is the most common internal modification of eukaryotic messenger RNAs, and recent findings have shown that m6A plays an important role in regulating the expression of both host and viral genes. The involvement of m6A writers, erasers and readers in regulating RNA stability, translation, splicing and degradation has been shown to regulate multiple stages of the viral life cycle. Previous studies have shown that persistent viruses, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV), Epstein–Barr virus (EBV), cytomegalovirus (CMV) and Kaposi's sarcoma-associated herpesvirus (KSHV), hijack host m6A machinery to amplify viral replication, control latency and inhibit antiviral immune responses. Moreover, m6A remodeling of epitranscriptomes plays a role in immune escape, including by dampening innate immune sensing, blocking interferon signaling, decreasing antigen presentation, and driving immune tolerance, which all enable chronic infection. The results have revealed m6A regulatory processes as potential targets for novel antiviral therapies. There are, however, significant challenges to clinical translation due to the context-dependent functions of m6A, the virus-specific regulatory mechanisms, and the possibility of off-target effects. This review highlights the present understanding on the molecular machinery of m6A modification, how m6A modification is involved in viral replication and immune evasion, how it is involved in the regulation of persistent human viruses, and emerging therapeutic strategies targeting m6A modification. Lastly, the paper explores the potential for personalized antiviral therapies based on epitranscriptomic profiling, multi-omics technologies, and AI to improve long-term clinical outcomes and overcome the limitations of existing treatment strategies in persistent viral infections.

1. INTRODUCTION

Persistent viral infections are a serious health problem worldwide: they reside for long periods in the host, escaping the immune system and never being completely cleared. Human viruses, including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), Epstein–Barr virus (EBV), human papillomavirus (HPV), cytomegalovirus (CMV) and Kaposi's sarcoma associated herpesvirus (KSHV), have developed intricate mechanisms allowing for the survival in the host, latent infection and reactivation (1,2). These strategies not only enable chronic infection, but also lead to immune dysfunction, tissue damage, and the development of virus-associated malignancies. While antiviral therapies have greatly improved disease management, viral persistence and immune escape remain key challenges for achieving total viral clearance and therapeutic success in the long-term (3,4).

Over the past few years, the study of reversible chemical modifications of RNA and their regulatory functions in gene expression has turned into a rapidly growing subfield, known as epitranscriptomics. The N6-methyladenosine (m6A) modification is among over 170 such modifications that have been discovered in RNA, and is the most prevalent internal modification found in the mRNA of eukaryotic cells and in many viral RNAs. These processes of deposition, removal and recognition of m6A are regulated by specialized proteins called "writers," "erasers" and "readers," which all contribute to the stability of the RNA, splicing, nuclear export, translation efficiency and degradation of the RNA. More evidence has emerged to support the idea of many viruses exploiting the host machinery for m6A to optimise their replication cycles while at the same time regulating host antiviral responses (5,6,7).

Importantly, m6A modification has been identified as a key moderator of viral immune evasion mechanisms, through its role in the regulation of innate immune sensing, interferon signaling, antigen presentation, and adaptive immune responses. Persistent viruses can escape immune recognition, become latent and persist chronically in the face of strong immune defenses through selective epitranscriptomic remodeling. These findings have sparked many studies focused on exploiting the pathways of m6A as new therapeutic avenues for antiviral therapies. Yet, m6A's complex and context-specific functions pose distinct translational challenges

in the clinic such as off-target effects, host toxicity and virus-specific regulatory variations. Current knowledge about how RNA m6A modifications contribute to viral immune evasion, their role in persistent human viral infections, and the challenges of current antiviral strategies, as well as opportunities for future precision antiviral therapy based on epitranscriptomic regulation is summarized (8,9,10).

2. MOLECULAR MACHINERY OF RNA M6A MODIFICATION IN VIRAL INFECTION

N6-methyladenosine (m6A) is the most common internal epitranscriptomic modification of eukaryotic messenger RNA and is now recognized as an important regulator of host and viral gene expression. Unlike permanent genetic changes, m6A is a reversible and dynamic chemical modification that allows for fast adaptation to physiological and pathological conditions, such as viral infection. The m6A landscape is formed by the concerted activities of three functional groups of proteins: methyltransferases (m6A "writers"), m6A demethylases (m6A "erasers"), and m6A-binding proteins (m6A “readers”). These regulators collectively regulate the fate of the RNA through mechanisms of transcript stability, alternative splicing, nuclear export, translation efficiency and degradation (11,12,13).

METTL3 and METTL14 are the main components of the core complex of the methyltransferase, and other proteins like regulatory proteins, including WTAP, VIRMA (KIAA1429), RBM15, and ZC3H13, play a role in the catalysation and specificity of the complex. In contrast, the m6A removal enzymes FTO and ALKBH5 provide an on/off switch for RNA metabolism in response to changes in the environment and cell. After methylation, reader proteins such as the YTH domain family (YTHDF1–3, YTHDC1/2) and IGF2BP family, recognize m6A modified transcripts and influence their biological outcomes by stimulating the translation, stabilizing the RNA or enhancing the transcript decay (14,15,16).

Many human viruses persistently infect human cells and actively hijack the m6A machinery in order to promote viral replication and persistence. It has been found that viral RNAs are often modified by m6A, which promotes viral protein production, viral genome replication, latency-reactivation cycles and inhibits antiviral immune signaling. In addition, viruses can affect the expression or activity of the host writers, erasers and readers, creating an intracellular environment conducive to long-term infection. It has now been established that viral adaptation, immune evasion and disease progression is a major process regulated by the dynamic interaction between the viral genome and the host m6A regulatory network (17,18,19).

Table 1. Major components of the RNA m6A regulatory machinery and their biological functions during viral infection (20,21).

Regulatory Group	Representative Proteins	Primary Biological Function	Role in Viral Infection
Writers	METTL3, METTL14, WTAP, VIRMA, RBM15, ZC3H13	Catalyze m6A deposition on RNA	Regulate viral RNA methylation, replication, and gene expression
Erasers	FTO, ALKBH5	Remove m6A modifications	Fine-tune viral RNA stability and replication dynamics
Readers	YTHDF1, YTHDF2, YTHDF3, YTHDC1, YTHDC2, IGF2BP1–3	Recognize m6A-modified RNA and determine RNA fate	Control viral RNA translation, stability, immune evasion, and persistence
Overall outcome	Coordinated writer–eraser–reader network	Dynamic regulation of RNA metabolism	Facilitates viral adaptation, persistence, and modulation of host antiviral responses

3. RNA M6A-MEDIATED REGULATION OF VIRAL REPLICATION AND PERSISTENCE

The recently identified N6-methyladenosine (m6A) modification of RNA has been recognized as a critical post-transcriptional control point in the viral lifecycle that can influence various aspects of viral replication and persistence. After incorporation onto viral RNA, m6A regulates viral fitness in infected cells by affecting transcript stability, translation efficiency, viral genome replication and trafficking in infected cells. The remodifiable feature of m6A allows viruses to quickly adjust to changing host environments and immune pressures, providing a dynamic way of maintaining chronic infection (22,23,24).

Evidence is growing that the effects of m6A are both highly virus-specific and context-dependent. In HIV, m6A modification promotes viral RNA export and protein synthesis, promoting efficient viral replication. The m6A modification is found to regulate the levels of viral protein expression and DNA synthesis in hepatitis B virus (HBV) by modulating the stability of viral transcripts and pregenomic RNA. Likewise, m6A is used by hepatitis C virus (HCV) to enhance RNA replication and to regulate interactions with host RNA-binding proteins. Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV) and cytomegalovirus (CMV) are members of the herpes virus family that rely on m6A-mediated regulation to promote productive replication and to maintain latent infection during long-term persistence and periodic reactivation. In addition, human papillomavirus (HPV) uses m6A modifications to control the expression of its oncogenic proteins that are responsible for cellular transformation and viral transcript processing (25,26,27).

More importantly, the regulation of m6A isn't limited to regulating viral RNA metabolism but also affects modulation of host cellular pathways that can indirectly contribute to viral persistence. Viruses change the RNA decay processes, stress responses and protein

translation, creating conditions inside the cell that are ideal for their longterm survival and suppression of immune mediated elimination. These varied roles of m6A within persistent human viruses strongly point to its pivotal role as a molecular switch that regulates replication, latency and reactivation. Therefore, the study of virus-specific m6A regulatory mechanisms gives further insights into the molecular mechanisms of persistent infections and new targets for novel antiviral therapeutics (28,29).

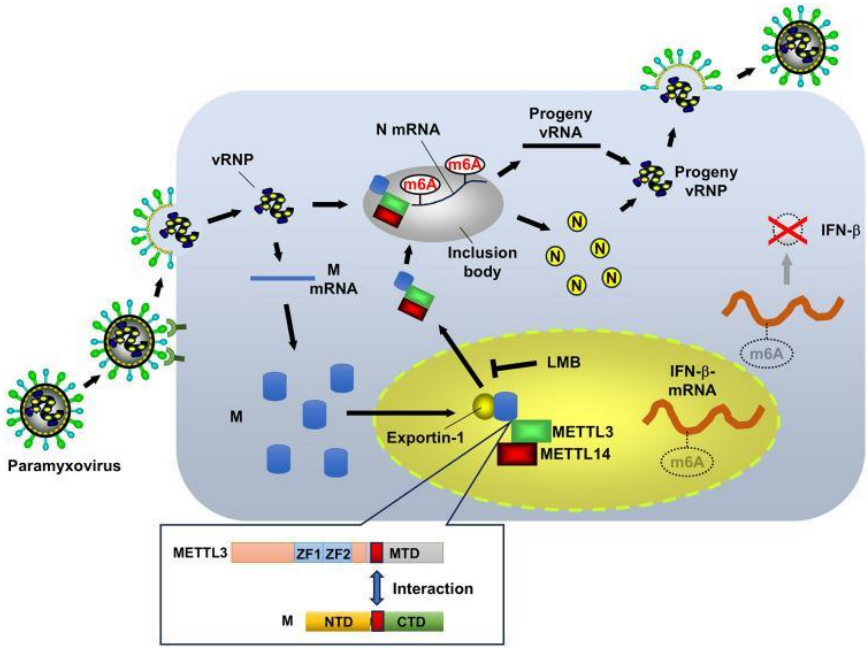

Figure 1. RNA m6A-mediated mechanisms regulating viral replication, RNA metabolism, and persistence.

4. RNA M6A MODIFICATIONS AS DRIVERS OF VIRAL IMMUNE ESCAPE

One of the unique properties of persistent viral infections is immune evasion, which allows viruses to survive the immune system. In recent years, it has been discovered that RNA N6-methyladenosine (m6A) modification is a crucial mechanism of the epitranscriptome, which allows viruses to escape immune destruction by regulating both viral and cellular RNAs. The remodeling of the epitranscriptomic landscape enables viruses to evade immune recognition and support efficient replication and persistence (30,31).

One of the major mechanisms is the impairment of innate immune sensing of viral RNA, especially through the cytosolic PRRs melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene I (RIG-I), thus limiting the activation of the downstream antiviral signaling pathways. This leads to reduced activation of interferon regulatory factors (IRFs) 3 and 7, as well as nuclear factor-κB (NF-κB) and reduced interferon type 1 and interferon stimulated genes (ISGs). This is a downside to their weakened antiviral response, leaving a good environment for persistent virus replication (32,33).

In addition to innate immune system, m6A also plays a role in adaptive immune system. Epitranscriptomic regulation results in decreased expression of viral antigen and host immune molecules that are essential for major histocompatibility complex (MHC) mediated antigen presentation and thus viral antigen-specific $CD8^+$ cytotoxic T lymphocyte (CTL) activation. Moreover, during chronic infection, m6A-mediated control of cytokine expression and immune checkpoint pathways leads to T-cell dysfunction and immune exhaustion. There are also a number of persistent viruses that use m6A to inhibit the natural killer (NK) cell-mediated cytotoxicity, which in turn leads to immune tolerance and viral latency. Taken together, these studies reveal that m6A is a multifaceted immune escape regulator that simultaneously suppresses antiviral signaling, immune cell activation and promotes long-term viral persistence, suggesting its potential as a promising antiviral immunotherapeutic target (34,35,36).

Table 2. Major mechanisms by which RNA m6A modifications promote viral immune escape

Immune Mechanism	m6A-Mediated Effect	Biological Consequence
Innate immune sensing	Reduced recognition of viral RNA by RIG-I and MDA5	Delayed initiation of antiviral responses
Interferon signaling	Suppression of IRF3/IRF7 activation and decreased type I IFN production	Impaired antiviral defense and enhanced viral replication
Interferon-stimulated genes (ISGs)	Downregulation of ISG expression	Reduced restriction of viral infection
Antigen presentation	Modulation of MHC-associated antigen processing and presentation	Decreased activation of virus-specific $CD8^+$ T cells
Natural killer (NK) cell activity	Reduced susceptibility to NK cell-mediated cytotoxicity	Increased viral persistence and latency

Adaptive immunity	Promotion of T-cell dysfunction and immune exhaustion	Maintenance of chronic infection and immune tolerance

5. VIRUS-SPECIFIC M6A REGULATORY NETWORKS: COMPARATIVE INSIGHTS ACROSS PERSISTENT HUMAN VIRUSES

As an evolutionarily conserved epitranscriptomic regulation mechanism, the regulation roles of N6-methyladenosine (m6A) modification vary greatly between persistent human viruses, depending on genome organization, replication, and interaction with the host cell. Instead of exerting general effects, m6A creates virus-specific regulatory networks that regulate virus gene expression, viral efficiency of replication, immune evasion, and virus latency. These disparities emphasize the intricacy of the m6A biology and the need for virus-specific therapeutic strategies (37,38).

In human immunodeficiency virus (HIV), m6A modification promotes greater nuclear export, translation and replication of viral RNA through interaction with host reader proteins. Hepatitis B virus (HBV) uses m6A to modulate the stability of pregenomic RNA and the reverse transcription process leading to viral DNA synthesis and chronic infection. In the case of hepatitis C virus (HCV), m6A regulates the process of RNA replication and also regulates the interaction between HCV RNA and host antiviral proteins. Human papillomavirus (HPV) exploits m6A to regulate viral transcript splicing and the production of virus oncogenic proteins (e.g. E6 and E7) that promote viral persistence and malignant transformation (39,40).

The m6A-dependent regulatory mechanisms are more diversified in herpesviruses, which can switch between latent and lytic cycles. Epstein–Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) exploit m6A to control the expression of latency-associated transcripts, viral reactivation and immune evasion. Likewise, cytomegalovirus (CMV) modifies host's m6A pathways to promote viral protein production and inhibit innate antiviral signalling. However, although there are differences in these viruses, a shared feature is the way that m6A is able to ensure effective viral replication while simultaneously mechanisms that limit immune recognition and promote long-term persistence. The comparative analysis of these regulatory networks also offers a powerful clue into conserved epitranscriptomic pathways that may be useful in the development of broad spectrum antiviral drugs, as well as the identification of unique molecular signatures that could be exploited for precision antiviral drug design that is specific to individual viral pathogens (41,42,43).

TABLE 3. COMPARATIVE ROLES OF RNA M6A MODIFICATIONS IN PERSISTENT HUMAN VIRUSES (44,45).

Virus	Major m6A-Regulated Process	Contribution to Viral Persistence	Immune Escape Mechanism
HIV	RNA export, translation, and replication	Sustained viral replication	Reduced innate immune activation and enhanced viral protein expression
HBV	Pregenomic RNA stability and reverse transcription	Maintenance of chronic infection	Attenuation of interferon-mediated antiviral responses
HCV	Viral RNA replication and RNA stability	Efficient intracellular replication	Modulation of host antiviral signaling pathways
HPV	Viral RNA splicing and oncogene (E6/E7) expression	Persistent infection and carcinogenesis	Reduced immune recognition of infected cells
EBV	Regulation of latent and lytic gene expression	Maintenance of latency and periodic reactivation	Suppression of adaptive immune responses
KSHV	Latency-associated transcript regulation	Long-term viral persistence	Immune evasion during latency and reactivation
CMV	Viral protein synthesis and host RNA remodeling	Productive infection and lifelong persistence	Inhibition of innate immune signaling and NK-cell responses

6. THERAPEUTIC TARGETING OF RNA M6A PATHWAYS: OPPORTUNITIES AND CURRENT LIMITATIONS

With the increasing understanding of the role of N6-methyladenosine (m6A) in viral replication and immune escape, the m6A regulatory machinery has emerged as an attractive target for the design of next-generation antiviral drugs. Modulation of host epitranscriptomic pathways can disrupt several stages of the viral life cycle and can provide a way to restore antiviral immunity as well, unlike antiviral drugs that specifically target viral proteins. In light of this, more and more research has been conducted to identify medications that could interact with m6A writers, erasers and readers (46,47).

One such strategy has garnered significant attention, the inhibition of the methyltransferase METTL3, which has a key role in the establishment of m6A modifications of both host and viral RNAs. Several persistent viruses have been shown to be suppressed by experimental METTL3 inhibitors, which also have the capability to modify viral gene expression. Likewise, small-molecule inhibitors against the demethylase FTO have been found to possess antiviral activity by interfering with the metabolism of viral RNA and by stimulating innate antiviral immune responses. Other therapeutic approaches involve modulation of ALKBH5 activity, RNA-based therapeutics, and nanoparticle-assisted delivery systems to selectively target and regulate m6A pathways in infected cells, and CRISPR-mediated epitranscriptomic editing (48,49).

Although these exciting developments make significant progress, there are some obstacles that remain to clinical translation of m6A-targeted therapies. Therefore, loss of specificity can lead to unwanted side effects, cell toxicity and interference with important

cellular functions due to the fact that thousands of host transcripts are regulated by m6A. Moreover, the biological repercussions of m6A modification vary significantly across viruses and even different phases of the life cycle of the same virus, making it hard to achieve universal therapeutic strategies. Other constraints include partial knowledge of the networks of m6A modification across different viruses, differences in patient populations, and the possibility of the development of viral adaptive mechanisms to circumvent epitranscriptomic inhibition. Thus, new therapeutics will need to be extremely context-specific and to be able to specifically disrupt viral persistence and immune escape without interfering with the normal regulation of host RNA (50,51,52,53).

7. PRECISION ANTIVIRAL THERAPY: INTEGRATING RNA M6A BIOLOGY INTO PERSONALIZED MEDICINE

Precision medicine has revolutionised the way infectious diseases are managed, focusing on personalised therapeutic interventions that are guided by molecular markers and other factors, instead of standardised protocols. Given the challenges in treating persistent viral infections, the incorporation of RNA N6-methyladenosine (m6A) biology into precision antiviral therapy is a promising avenue for enhanced therapy efficacy and reduced adverse effects. Due to the heterogeneity of the epitranscriptomic profile of different viruses, tissues and patients, defining virus-specific and patient-specific signatures of m6A modifications could enable personalized therapeutic strategies. Recently, high-throughput sequencing approaches, such as MeRIP-seq, direct RNA sequencing, and single-cell transcriptomics were developed, allowing the systematic characterization of m6A modifications in viral and host RNA (54,55,56). With these technologies, the identification of biomarkers of the epitranscriptomic changes that are linked to viral persistence, immune escape, disease progression and treatment response can be realised. Beyond that, multi-omics integration of genomics, transcriptomics, proteomics and epitranscriptomics data enables a more comprehensive understanding of host–virus interactions, which is useful for the identification of novel therapeutic targets and predictive biomarkers. Recently, artificial intelligence (AI) and machine learning algorithms have proven to be useful tools for deciphering complex epitranscriptomic datasets. Functional m6A sites can be identified by predictive computational models, therapeutic responses can be estimated in a patient-specific manner, and patient-specific antiviral treatment strategies can be optimized. Furthermore, combination therapy of simultaneous targeting of viral proteins and host immune pathways and m6A regulatory components may decrease the risk of antiviral resistance and increase immune-mediated viral clearance. However, standardized methods for epitranscriptomic profiling, large-scale clinical validation studies, and understanding of temporal dynamics of m6A regulation during infection are required for successful implementation of precision antiviral medicine (57-61). As these obstacles are overcome, the application of m6A biology in personalized antiviral therapy holds great potential to transform the clinical management of chronic viral infections by facilitating the more accurate diagnosis of infections, selection of personalized antiviral therapy and enhanced long-term clinical outcomes (62,63).

Table 4. Emerging precision medicine approaches integrating RNA m6A biology for persistent viral infection (57,58).

Precision Strategy	Technology/Approach	Potential Clinical Application
Epitranscriptomic profiling	MeRIP-seq, direct RNA sequencing	Identification of virus-specific m6A signatures and biomarkers
Single-cell analysis	Single-cell RNA sequencing (scRNA-seq)	Characterization of cellular heterogeneity and viral persistence mechanisms
Multi-omics integration	Combined genomics, transcriptomics, proteomics, and epitranscriptomics	Discovery of therapeutic targets and patient stratification
Artificial intelligence	Machine learning and predictive algorithms	Prediction of functional m6A sites and individualized therapeutic responses
Targeted epitranscriptomic therapy	Selective modulation of METTL3, FTO, ALKBH5, and reader proteins	Personalized inhibition of virus-specific m6A pathways
Combination antiviral therapy	Integration of m6A-targeted agents with conventional antivirals and immunotherapies	Enhanced viral clearance, reduced resistance, and improved long-term treatment outcomes

8. FUTURE PERSPECTIVES AND CONCLUSION

The rapidly developing discipline of viral epitranscriptomics has revolutionized understanding of molecular mechanisms underlying chronic viral infection. N6-methyladenosine (m6A) is one of the various modifications identified to date with critical roles in viral replication, latency, immune evasion and host antiviral responses. Although great strides have been made in understanding the biological roles of m6A, the roles of epitranscriptomic regulation in viral infections are not fully understood. There is a need for future studies to establish the temporal and spatial evolution of m6A modifications during viral infections and in various cell types. These new technologies, including single-cell sequencing, spatial transcriptomics, direct RNA sequencing, and high resolution epitranscriptomic mapping, will provide insights into previously unrecognized regulatory mechanisms that are implicated in viral persistence and disease progression.

At the same time, there is a very promising research direction of the development of highly selective modulators of m6A writers, erasers and readers which can be used to develop a new generation of antiviral drugs. Better specificity will be necessary for

successful clinical translation to minimize off-target effects while maintaining important RNA functions in the host. Combining epitranscriptomic profiling with AI, multi-omics and precision medicine will further facilitate personalised therapeutic strategies based on the type of virus and the molecular profile of the patient.

Overall, it is clear that m6A modification of RNA is a hub molecule linking viral replication, immune evasion and chronic infection. Human viruses have developed complex strategies to hijack host m6A machinery, which allow viruses to increase their fitness and to dampen antiviral immunity. Such detailed understanding of these complex regulatory networks not only gives a better understanding of virus–host interactions but also opens up novel therapeutic possibilities to fight against persistent viral diseases. Future molecular virology, immunology, epitranscriptomics and computational biology studies will be critical for translating these advances into practical precision antiviral treatments that could break through existing antiviral treatment barriers and enhance clinical outcomes over the long term.

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