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m⁶A methylation: a potential key player in understanding and treating COVID-2019 infection

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Since its discovery in 2019, coronavirus disease 2019 (COVID-2019) spans a wide clinical spectrum from the asymptomatic stage, mild infection, to severe pneumonia. In patients with COVID-2019, factors such as advanced age, diabetes, or hypertension are associated with a significantly increased risk of severe diseases and death. Of note, the mechanisms underlying differences in the risk and symptoms of COVID-2019 among different populations are still poorly characterized. Accordingly, it is imperative to elucidate potential pathophysiological mechanisms and develop targeted therapeutic approaches for COVID-2019 infection. N⁶-methyladenosine (m⁶A) is one of the most common modifications in mammalian RNA transcripts and is widely found in messenger RNAs and some non-coding RNAs. It has been reported that m⁶A methylation modifications are present in viral RNA transcripts, which are of great significance for the regulation of the viral life cycle. Furthermore, m⁶A methylation has recently been found to be strongly associated with COVID-2019 infection. Therefore, this article reviews recent advances in studies related to the role of m⁶A methylation in COVID-2019 infection.

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FACTS

1. This article systematically reviews research on m⁶A and COVID-2019 infection;
2. This article proposes potential future research directions on the relationship between m⁶A and COVID-2019 infection in the context of existing research.

OPEN QUESTIONS

1. This article suggests a mathematical model based on m⁶A-related genes for the prediction of COVID-2019 infection;
2. This article proposes a treatment strategy for COVID-2019 infection based on m⁶A-related pathways.

INTRODUCTION

The novel coronavirus is an RNA virus that belongs to the family Coronaviridae and is a close relative of the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), whose full name is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. This virus is the

pathogen causing coronavirus disease 2019 (COVID-19) [2]. COVID-19 is a highly infectious and lethal disease that is majorly transmitted between individuals through respiratory droplets and contact routes and has caused hundreds of millions of infections and millions of deaths worldwide, for which there is no specific treatment [3–7]. Some drugs, such as remdesivir, chloroquine, and hydroxychloroquine, have been used in the treatment of COVID-19 [8], but their efficacy and safety still require further research. Currently, COVID-19 patients are mainly treated with supportive care, including oxygen therapy, fluid infusion, and organ support, which aims to enable patients to recover as well as possible [9]. It has become a hot research topic to investigate the pathogenesis of COVID-19 at the molecular level and identify reliable therapeutic targets.

N⁶-methyladenosine (m⁶A) is a common RNA modification and widely exists in cells [10]. m⁶A involves the addition of methyl groups to RNA molecules and plays an important role in biological processes such as transcription, translation, and splicing of RNA [11–13]. Recently, mounting evidence has revealed that m⁶A methylation modifications are closely related to virus infection [14–19]. As many studies demonstrated, m⁶A methylation can affect cellular function through various mechanisms during the occurrence of hepatitis virus, human immunodeficiency virus type 1, and SARS-CoV-2 infection to adapt to the life cycle demands of the virus [15, 16, 18, 20–23]. In turn, m⁶A methylation can also have an impact on viral infection, affecting the life cycle and pathogenicity of the virus [20, 24, 25]. Therefore, elucidating the

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specific mechanism of m⁶A methylation in COVID-19 virus infection is important for the prevention and treatment of COVID-19.

RNA M⁶A METHYLATION

Overview of m⁶A

RNA m⁶A methylation refers to a methylation modification that occurs at the nitrogen-6 position of the adenine (A) base on RNA molecules, which is widely found in eukaryotic ribosomal messenger RNA (mRNA), transfer RNA (tRNA), RNA (rRNA), and noncoding RNA (ncRNA) and has been shown to be important in regulating various biological processes of RNA [10, 26, 27]. As one of the most common RNA modifications, m⁶A methylation occurs mainly in the shared sequence RRACH (R = G or A; H = A, C, or U) and is mostly enriched in the stop codon, 3' untranslated region, and long internal exons, which is dynamically reversible under the regulation of various modifying enzymes, such as methyltransferases (writers), demethylases (erasers), and methylated readers (readers) [28]. m⁶A methylation is catalyzed by methyltransferases. Furthermore, two methyltransferases have been identified to be involved in m⁶A methylation, including methyltransferase-like 3 (METTL3) and METTL14 [29]. In addition, other proteins, such as WTAP, KIAA1429, and RBM15, are also implicated in the mediation of m⁶A methylation [30]. m⁶A readers are a class of proteins that recognize and bind to m⁶A-modified RNAs, which include many proteins, such as YTHDC1, YTHDC2, YTHDF1, YTHDF2, YTHDF3, HNRNPC, and IGF2BP1 [31]. These proteins can regulate biological processes of RNA, including transcription, splicing, translation, and degradation [31–33]. Demethylases can reverse the m⁶A methylation of RNA by reducing the m⁶A modification to A. A variety of demethylases have been identified, including FTO and ALKBH5, which are involved in RNA metabolism and regulation and are essential for maintaining RNA stability and function [33]. m⁶A recognition factors are a class of RNA structural domains capable of recognizing and binding to m⁶A modifications, which consist of YTHDC1, YTHDC2, YTHDF1, YTHDF2, and YTHDF3.

Moreover, m⁶A recognition factors participate in the recognition and interaction to RNA and modulate the local structure and interaction of RNA [34].

M⁶A AND COVID-2019 INFECTION

Effects of m⁶A methylation on COVID-2019 infection

Accumulating evidence has unraveled that m⁶A modification is crucial for the transmission and pathogenicity of COVID-2019. For instance, Liu et al. found that m⁶A modification was deregulated in host cells infected with SARS-CoV-2 and re-localized by viral infection, thereby increasing the abundance of m⁶A in cells [17]. Campos et al. identified the methylation of m⁶A transcripts in African green monkey Vero cells and human Calu-6 cells infected with SARS-CoV-2 with RNA sequencing and analyzed the results with nonparametric statistics and two computational methods (m6anet and EpiNano), which showed higher levels of m⁶A methylation in the RNA of infected cells [35]. This study verifies that the effect of SARS-CoV-2 virus infection on cell function is associated with m⁶A methylation. Qiu et al. observed down-regulation of m⁶A-related genes in blood leukocytes from COVID-2019 patients [36]. In addition, a study by Li et al. showed that the m⁶A methylation gene METTL3 was significantly downregulated and inflammatory genes were upregulated in lung tissues of patients with severe COVID-2019 than in those of healthy individuals [16]. Additionally, Lu et al. analyzed the expression of 9 writers, 15 readers, and 2 erasers for m⁶A modification in healthy individuals and COVID-2019 patients and observed that the expression of WTAP, RBM15, HNRNPC, YTHDC1, FMR1, HNRNPA2B1, ELAVL1, and YTHDF3 was markedly higher but the expression of RBM15B, IGF2BP2, and IGF2BP1 was substantially poorer in COVID-2019 patients than in healthy individuals, illustrating that the above targets may be associated with the regulation of m⁶A on COVID-2019 infection [37] (Fig. 1). Subsequent research further validated that SARS-CoV-2 infection altered the epigenetic transcriptome of m⁶A in lymphocytes, especially in those from patients with severe disease, and that it could enhance RBM15 m⁶A modification to regulate host immune responses [38].

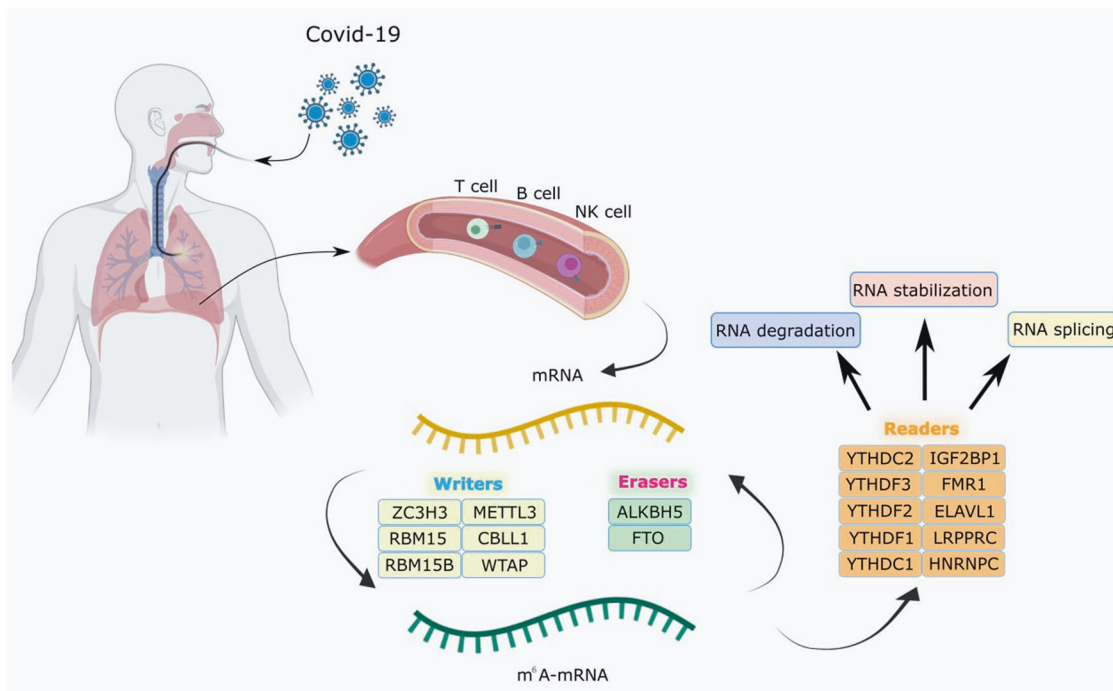


Fig. 1 The overview of m⁶A RNA methylation modification in blood lymphocytes of patients infected with SARSCoV-2, including writers, readers, and erasers.

The pathogenesis of severe respiratory infections caused by novel coronaviruses is associated with a disorder of the pro-inflammatory/anti-inflammatory response and immune imbalance, with immune system overreaction, excessive apoptosis and depletion of immune cells, immunosuppression, and immunoparalysis as the main immunopathological manifestations. For instance, prior research revealed that patients with severe COVID-2019 had high levels of pro-inflammatory cytokines than patients with moderate COVID-2019, indicating that high levels of pro-inflammatory cytokines are associated with the poor prognosis of COVID-2019 patients [39, 40]. Braun et al. found peak reactivity of CD35 T cells in 4% of COVID-2019 patients and 19% of healthy controls, illustrating the existence of T cell cross-reactivity which may prevent SARS-CoV-2 infection to some extent [41]. Because persistent inflammatory factor storms serve as one of the most dangerous factors in the COVID-19 pandemic, pro-inflammatory cytokines such as IL-1 α , IL-1 β , IL-6, and TNF- α play a key role in COVID-19 development. Recent studies have indicated that m⁶A modification can affect SARS-CoV-2 infection by regulating the antiviral response of immune cells. A previous study exhibited that METTL3 was downregulated in host cells after SARS-CoV-2 infection to decrease m⁶A levels in viral and host genes, thus enhancing retinoic acid-inducible gene-1 binding and the expression of downstream innate immune pathways and inflammatory genes, suggesting that human immune responses play an important role in COVID-2019 infection [42]. A study by Du et al. unraveled that deletion of the m⁶A-related target METTL14 or YTHDF1 in macrophages predisposed infected mice to inflammatory factor storms, resulting in higher mortality from infection, which illustrated m⁶A as a pivotal mechanism regulating inflammatory factor storms [43]. In summary, the immune response participates in the development and progression of COVID-2019. As an important biomolecule, m⁶A not only is essential for gene expression, translation, and regulation but also exerts important physiological functions in various aspects of immune responses in the body. The role of m⁶A in the immune system has been investigated, which provides not only a novel perspective for the in-depth understanding of the biological function of m⁶A but also a critical reference for exploring the occurrence, transmission, prevention, and control of COVID-2019 [44–46]. However, there is a lack of research on the association of m⁶A with immune responses in COVID-2019 infections. In this context, further research is warranted to characterize the regulatory mechanism of m⁶A in immune cells and the potential molecular mechanism of interactions between m⁶A and COVID-2019 infection-related immune responses, thus providing new ideas and approaches for the treatment and prevention of COVID-2019.

Effect of m⁶A methylation modification on the evolution of SARS-CoV-2

It has been demonstrated that m⁶A methylation modifications also play a crucial role in the transmission and evolution of SARS-CoV-2. Liu et al. used RNA immunoprecipitation sequencing for sequencing of the m⁶A methylation profiles in SARS-CoV-2-infected human and monkey cells and systematic bioinformatics analysis and found the dynamic distribution pattern of m⁶A modifications in the SARS-CoV-2 genome and that m⁶A modifications were also widely present on the negative-strand RNAs as replication intermediates. Further, the researchers used the more precise m⁶A individual-nucleotide-resolution cross-linking and immunoprecipitation technique to identify m⁶A sites at single-base resolution on SARS-CoV-2 genomic RNA and identified eight m⁶A sites at single-base resolution, and more importantly, phylogenetic analysis unveiled that a series of mutant strains carrying specific m⁶A modification site emerged in different regions of the world. Functional experiments confirmed that the m⁶A methyltransferase METTL3/14 and the demethylase ALKBH5

negatively/positively regulated the replication of the SARS-CoV-2 genome, respectively, and that a decrease in the m⁶A reading protein YTHDF2 also promoted viral replication and infectivity. As this result indicated, SARS-CoV-2 infection not only elevates m⁶A contents in the host genome and changes the overall methylation profile. Meanwhile, SARS-CoV-2 can also use cellular enzymes for its own methylation to generate an evolutionary pressure to adapt the viral DRACH sequence, thus becoming more similar to the cellular sequence to successfully evade the killing effect of interferon. In conclusion, m⁶A modifications affect the interaction between the host and SARS-CoV-2 [17]. The research by Wyler et al. also revealed that m⁶A methylation is vital for virus-host interactions [47]. It was found in the research by Zhang et al. that METTL3A expression was increased and its distribution in cells was changed after SARS-CoV-2 infection. This research also confirmed the effect of METTL3 on viral replication by knocking down or overexpressing METTL3 through transfection with short hairpin RNA or plasmids [25].

m⁶A METHYLATION MODIFICATIONS AND DIAGNOSIS OF SARS-COV-2 INFECTION

The importance of m⁶A in COVID-2019 infection was previously confirmed. Accordingly, molecular mechanisms underlying m⁶A can be used for the development of new preventive and therapeutic options for COVID-2019. In the study by Lu et al., a model to predict the risk of COVID-2019 was constructed by screening m⁶A-related genes, which successfully predicted the degree of risk of COVID-2019 infection and had a high validity [48]. In the study by Qing et al., 18 basic m⁶A methylation enzymes were identified, among which the eight optimal m⁶A methylation enzymes were selected to predict the occurrence of COVID-2019 with a random forest model which had high-accuracy prediction capability [41]. As a result, the risk of COVID-2019 infection can be assessed by constructing a linear model of m⁶A-related genes. In addition, Dong et al. used LASSO and multivariate Cox regression analyses to determine prognostic factors for patients with COVID-2019 and found that hypertension, increased neutrophil-to-lymphocyte ratio, and elevated NT-proBNP were significantly associated with the poor in-hospital prognosis of COVID-2019 patients. The model involving these three factors effectively predicted the in-hospital survival of COVID-2019 patients, which, therefore, is expected to be applied to the clinical management of COVID-2019 [49]. Therefore, the prediction models of m⁶A-related genes constructed based on clinical symptoms would be expected to more accurately predict disease onset and progression in the early stages of COVID-2019 infection.

m⁶A METHYLATION MODIFICATION AND TREATMENT OF SARS-COV-2 INFECTION

As reported, m⁶A-related regulators in SARS-CoV-2 infection provide new strategies for the development of vaccines and antiviral drugs. Specifically, m⁶A modification-related genes are knocked down or overexpressed to reduce viral virulence, thus designing attenuated vaccine viruses. Additionally, the mechanisms of m⁶A modification can be utilized as a new target for antiviral therapy, such as the method investigated by Aik et al. [50]. Malacrida et al. [51] reported a variety of m⁶A demethylation-related small molecules, such as N-oxalylglycine (NOG), 2,4-Pyridinedicarboxylic acid (2,4-PDCA), IOX3, and MV1035, providing ideas for the development of drugs involving m⁶A-related targets. Liu et al. found that knockdown of METTL3, METTL14, and YTHDF2 increased viral replication, whereas knockdown of ALKBH5 repressed SARS-CoV-2 infection [17]. Therefore, drugs targeting these relevant targets can be more effective in treating COVID-2019 infection. A study by Zannella et al. exhibited that emodin enhanced interference with the replication of β -coronavirus

replication, particularly SARS-CoV-2, and that its strong activity of anti-SARS-CoV-2 was associated with m⁶A pathways [52]. There are some reports on the antiviral effects of m⁶A-related small molecule drugs (such as NOG, 2,4-PDCA, IOX3, and imidazobenzoxazin-5-thione MV1035) against other viruses. Nevertheless, the development of m⁶A-related small molecule drugs against SARS-CoV-2 requires more in-depth research, which helps to increase the efficacy of treatment of COVID-2019 infection and provides novel ideas and methods to prevent similar outbreaks.

CONCLUSION AND OUTLOOK

With the global outbreak of the COVID-2019 epidemic, tremendous attention has been paid to the association between m⁶A methylation and COVID-2019 infection, and the involved mechanisms are being intensively explored. Although m⁶A methylation has been revealed to play a critical role in COVID-2019 infection, the detailed regulatory mechanisms still need in-depth studies. In addition, the development of m⁶A-related small molecule drugs against SARS-CoV-2 is also an important field, which needs to be intensively researched for more rapid and effective treatment of COVID-2019 infection to make a greater contribution to global human health security. In addition to the development of drugs targeting m⁶A methylation, research on other m⁶A-related molecular targets, such as reader proteins and demethylases, are also promising targets for vaccines and therapies against COVID-2019. In addition, as the understanding of m⁶A methylation gradually deepens, new therapeutic strategies may emerge, such as modulation of the immune response or suppression of inflammation by regulating m⁶A methylation modifications. Therefore, more vaccines and treatments targeting m⁶A methylation against COVID-2019 are expected to be developed in the future, providing new strategies and methods to control COVID-2019 outbreaks.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

SX, YC performed study concept and design; WQ, LD performed development of methodology and writing, review and revision of the paper; JZ, HW provided acquisition, analysis and interpretation of data, and statistical analysis; WQ, JZ finished manuscript editing. All authors read and approved the final paper.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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