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The role of m^{6}A RNA methylation in infectious diseases

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Among over 170 known RNA modifications, N^6-methyladenosine (m^{6}A) stands out as the most ubiquitous and extensively studied modification, found in different cellular RNA. The m^{6}A plays a pivotal role in regulating RNA nuclear export, stability, secondary structure, translation, and degradation eventually determining the gene expression. The m^{6}A modification is controlled by three classes of enzymes: "writers", "erasers", and "readers" which not only play a role in adding and removing the methyl group but also help in recognizing and interpreting the methylation marks. Although m^{6}A has been widely studied in the context of metabolic diseases and cancers, its influence on infectious diseases remains under-explored. The infection cycle of several pathogens, including viruses, bacteria, and parasites is regulated by the m^{6}A methylation machinery. In this review, we will not only explore the existing knowledge about m^{6}A methylation but also its influence in shaping the pathogen life cycle paving our way to therapeutic aspects to mitigate infectious diseases.

KEYWORDS

N^6-methyladenosine (m^{6}A), writers, erasers, readers, infectious diseases

1 Introduction

There are various RNA modifications that involve chemical alterations in RNA molecules, without changing the underlying sequences (Helm and Motorin, 2017), that regulate their expression and stability (Wang et al., 2015a). These modifications are collectively known as "epitranscriptomic modifications" (Helm and Motorin, 2017). With the recent advancement in technologies, more than 170 distinct RNA chemical modifications have been identified so far, in both coding and non-coding RNAs (Cappannini et al., 2024). Among these, some of the most extensively studied RNA modifications include N^6-methyladenosine (m^{6}A) found on eukaryotic mRNA (Desrosiers et al., 1974), 5-methylcytosine(m^{5}C) found on rRNA, tRNA, ncRNA and mRNA (Wei et al., 1975a), Pseudouridine(ψ) observed in tRNAs, rRNAs, and snRNA (Schwartz et al., 2014a), N^1-methyladenosine (m^{1}A) predominantly found on tRNA and rRNA (Wu et al., 2022), and N^4-acetylcytidine (ac^{4}C) detected in tRNA, rRNA, and recently on mRNA (Arango et al., 2018).

Among these, N^6-methyladenosine (m^{6}A) is the most common internal modification (Desrosiers et al., 1974), found in the higher eukaryotic RNAs (Horowitz et al., 1984). The pioneering research conducted by Desrosiers, Friderici, and Rottman in 1974 led to the discovery of m^{6}A methylation in polyadenylated RNA from Novikoff hepatoma cells (Desrosiers et al., 1974). The presence and biological significance of m^{6}A methylation was further confirmed in 1975 by Perry and Kelly (Perry et al., 1975). Herein, adenosine is methylated at the N^6 position (Desrosiers et al., 1975), which is incorporated both co-

transcriptionally (Zhou et al., 2019) and post-transcriptionally (Wang et al., 2015a). m^{6}A is highly conserved ranging from higher eukaryotes, plants, yeasts, and viruses (Gokhale et al., 2016a; Horowitz et al., 1984). The initial discovery methods for m^{6}A methylation include radiolabelled nucleosides, oligo(dT)-cellulose chromatography, poly(A) (−)RNA fractionation, enzymatic degradation, and resolution of nucleosides (Desrosiers et al., 1974; Perry et al., 1975). Recent progression in m^{6}A detection involves the use of m^{6}A-specific antibodies by methods such as methylated RNA immunoprecipitation sequencing (MeRIP-seq or m^{6}A-seq) (Schwartz et al., 2013), m^{6}A individual-nucleotide-resolution cross-linking and immunoprecipitation (miCLIP) (Linder et al., 2015), qPCR-based methods (Zhang J. et al., 2019), mass spectroscopy (Kim et al., 2021) and many more. These transcriptome-wide mappings have shown that the majority of the m^{6}A residues exhibit significant enrichment at the 3′ UTR and in proximity to stop codon (Dimock and Stoltzfus, 1977; Horowitz et al., 1984; Meyer et al., 2012; Schwartz et al., 2013). The predicted frequency of m^{6}A in RNAs is approximately ~three to five m^{6}A sites in every mRNA of mammals (Desrosiers et al., 1974). The consensus sequence for m^{6}A modification is characterized by the 5′-DRACH-3′(D = A/G/U, R = A/G, H = U/A/C) identified by the methyltransferase complex (Dominissini et al., 2012; Linder et al., 2015). m^{6}A plays a critical role in various biological processes including the regulation of mRNA stability (Wang Y. et al., 2014), control of mRNA translation (Meyer et al., 2015; Xiao et al., 2016), RNA splicing (Dominissini et al., 2012; Ping et al., 2014), mRNA export from the nucleus to cytoplasm facilitating their translation (Wickramasinghe and Laskey, 2015), embryonic development (Ping et al., 2014; Xiao et al., 2016), and in maintaining stem cell pluripotency and differentiation (Batista et al., 2014).

This multifaceted role of m^{6}A modification in regulating a variety of gene expressions has also been linked to the development and progression of multiple diseases. Dysregulation and abnormal cross-talk between m^{6}A writers (Li et al., 2019a), erasers (Hu et al., 2022; Huang et al., 2019; Zhang Z. et al., 2019), and readers (Chen H. et al., 2022; Christiansen et al., 2009) can lead to implications in myriad pathological disorders including cancer (Barbieri et al., 2017; Yang et al., 2019; Zhang et al., 2016), neurological (Chokkalla et al., 2019; Zhang S. et al., 2022) and metabolic disorders (Christiansen et al., 2009; Regué et al., 2019), aging-associated (Liu et al., 2021a), pulmonary (Ma et al., 2021a), cardiovascular diseases (Mathiyalagan et al., 2019; Xing-Bo et al., 2018), and a variety of infectious diseases. In recent years, extensive research has explored various diseases, but the impact of m^{6}A alterations in infectious diseases has not received much attention. This review will focus on recent advancements in understanding "the role of m^{6}A RNA methylation in infectious diseases" and provide compelling insights into m^{6}A as a potential therapeutic target. We will explore the diverse aspects of the pathogenicity of several infectious diseases including viral, bacterial, and parasitic infections along with their host-pathogen interactions. Exploring m^{6}A, in the context of infectious diseases may open new avenues in studying immune responses which holds promising diagnostic strategies, clinical implications, and potential treatment. To understand the intricate cross-talk within m^{6}A machinery, it is essential first to understand its main components.

2 Mechanism of the m^{6}A methylation

In eukaryotes, adenosine methylation at the N^6 position is predominantly carried out by three main protein complexes: "writers" (methyltransferases) (Agarwala et al., 2012; Bokar et al., 1994; 1997), "erasers" (demethylases) (Jia et al., 2011; Zheng et al., 2013), and "readers" (m^{6}A effector complex) (Dominissini et al., 2012; Theler et al., 2014; Xiao et al., 2016). "Writers" are responsible for adding the methyl group (Bokar et al., 1994), while "erasers" have an opposite function as they remove the methyl group by oxidative demethylation (Jia et al., 2011). "Readers" bind to the methylated mRNAs and alter their functions (Dominissini et al., 2012). They all work together and play an essential role in regulating the m^{6}A RNA methylome.

2.1 m^{6}A methyltransferase "writer" complex

The methyltransferase enzyme complex mainly includes METTL3, METTL14, and WTAP which is accountable for m^{6}A methylation. Inside the nuclear speckle, METTL3 serves as the core catalyst that transfers the methyl group from S-adenosylmethionine (SAM) to the targeted adenosine of mRNA (Bokar et al., 1997; Narayan and Rottman, 1988). METTL14 amplifies the catalytic efficiency of METTL3 by providing an RNA-binding scaffold(Wang et al., 2016). WTAP, though lacking catalytic function, but functions as an adapter and helps in the localization of methyltransferase complex (Agarwala et al., 2012; Ping et al., 2014). Several other enzymes such as METTL5 (van Tran et al., 2019), METTL16 (Pendleton et al., 2017), KIAA1429 (VIRMA) (Schwartz et al., 2014a), RNA binding motif15 (RBM15)/RBM15B (Patil et al., 2016), HAKAI, Zinc finger CCCH domain-containing 13 (ZC3H13) (Wen et al., 2018), and ZCCHC4 (Ma et al., 2019) have their individual role in the methylation process.

2.1.1 The METTL family

The METTL (Methyltransferase-like) family comprises of a group of enzymes that primarily work in the methylation of nucleic acids. The key members of the METTL family include METTL3 and METTL14 (Śledź and Jinek, 2016; Wang et al., 2016; Wang et al., 2014b). METTL3 was discovered in 1994 (Bokar et al., 1994), and subsequently, METTL14 was identified as an important component of methyltransferase complex (Liu et al., 2014a; Wang et al., 2016). Initially, METTL14 was thought to be a standalone methyl transferase catalysing m^{6}A methylation besides METTL3 (J. Liu et al., 2014b) however, subsequent research have clarified that METTL3 and METTL14 assemble into a 1:1 single heterodimeric complex (1 MDa) inside the nuclear speckle. Both METTL3 and METTL14 work cooperatively to enhance methyltransferases activity where only METTL3 is responsible for catalytic reaction typically occurring co-transcriptionally while the mRNA is being synthesized (Bokar et al., 1997; Ping et al., 2014; Sommer et al., 1978) and its interaction with mRNA is stabilised by the coiled-coil N-terminus of METTL14 (Śledź and Jinek, 2016; Wang et al., 2016; Wang et al., 2014b). In a study, knocking out either METTL14 or METTL3 in HeLa and 293FT cells results in decreased levels of m^{6}A methylation, indicating their importance in

this reaction (Dominissini et al., 2012; Liu et al., 2014b). Additional members of the METTL family which participate in m^{6}A RNA methylation processes are METTL4, METTL5, METTL7A and METTL16, etc. METTL16 methylates U6 snRNA, lncRNAs, and MAT2A mRNA, an enzyme that is crucial for SAM synthesis (Pendleton et al., 2017). It has the ability to methylate hairpin structures in MAT2A pre-mRNA, forming m^{6}A in a C-m^{6}A-G context regulating SAM homeostasis. It requires a specific RNA structure and the UACAGAGAA nonamer for its activity (Pendleton et al., 2017; Warda et al., 2017). METTL5, on the other hand, methylates the 18s rRNA at m^{6}A by forming a heterodimeric complex with TRMT112, vital for ribosome biogenesis and function. It is located in the nucleolus and impacts the translation of protein and cell growth (Ignatova et al., 2020; van Tran et al., 2019).

2.1.2 WTAP (Wilms Tumour-1-associated protein)

WTAP is universally expressed as a nuclear protein (Horiuchi et al., 2013) that plays an essential role in regulating the m^{6}A level in mRNA by interacting with METTL3 and METTL14 enzyme complex (Agarwala et al., 2012; Liu et al., 2014b; Ping et al., 2014; Zhong et al., 2008). It was initially identified in *Arabidopsis* (plant homolog, FIP37) (Zhong et al., 2008) followed by its characterization in yeast (yeast homolog, mum2) (Agarwala et al., 2012). Subsequently, the association between METTL3 and WTAP was identified in various types of mammalian cells (Liu et al., 2014b; Ping et al., 2014; Schwartz et al., 2014b). Although WTAP does not have catalytic activity, it is crucial for proper localization of METTL3 and METTL14 on the nuclear speckle as its knockout decreases m^{6}A content and causes tissue-specific defects, leading to apoptosis (Liu et al., 2014b; Ping et al., 2014). WTAP has also been linked to cancer, where its upregulation in over 30% of cases causes acute myeloid leukaemia (AML) (Bansal et al., 2014; Weng et al., 2018).

2.2 m^{6}A demethylases "eraser" proteins

The regulation of m^{6}A plays a pivotal role in RNA metabolism and function. This dynamic system involves a delicate interplay between methyltransferases, responsible for adding methyl groups (discussed earlier), and demethylases like FTO (Fat Mass and Obesity-associated Protein) (Jia et al., 2011) and ALKBH5 (α-Ketoglutarate-dependent Dioxygenase AlkB Homolog 5), (Zheng et al., 2013), which effectively remove them. These demethylases, alongside methyltransferases, determine the m^{6}A level and its functions (Meyer et al., 2012).

2.2.1 FTO

FTO, a protein related to obesity and an α-ketogluterate dependent Dioxygenase, was first identified as a demethylating enzyme for 3-meT (N^3-methylthymidine) in ssDNA (Gerken et al., 2007) and 3-meU (N^3-methyluridine) in RNA (Jia et al., 2008). It was later found to demethylate m^{6}A in mRNA (Jia et al., 2011) although, its activity on m^{6}A is exceptionally low compared to its resilient demethylation in m^{6}A.m. (Hess et al., 2013; Jia et al., 2011; Mauer et al., 2017) which is another modified nucleotide found at the 5′UTR in mRNA and snRNA (Mauer et al., 2017; Wei C.-M. et al., 1975). Knockout studies showed that the depletion of FTO significantly increases m^{6}A.m. but not m^{6}A levels (Hess et al., 2013). FTO participates in various biological functions, including the regulation of body mass, tumorigenesis, and pre-adipocyte differentiation (Cui et al., 2017; Fischer et al., 2009).

2.2.2 ALKBH5

ALKBH5, a component of the AlkB family, functions as an enzyme for demethylating m^{6}A modification in mRNA (Zheng et al., 2013). As indicated by its nuclear localization, its function in m^{6}A demethylation is crucial for mRNA biogenesis within the nucleus (Linder et al., 2015). ALKBH5 regulates m^{6}A levels in mRNA, with knockout increasing and overexpression decreasing the m^{6}A content respectively (Garcia-Campos et al., 2019). It also has an essential role in germ cell development, as evidenced by impaired spermatogenesis and fertility in ALKBH5-deficient male mice (Tang et al., 2018; Zheng et al., 2013). Notably, ALKBH5 is significant in viral response by regulating m^{6}A modification on viral transcripts and influencing host immune responses (Zheng et al., 2017). ALKBH5 also selectively demethylates m^{6}A on RNA-RNA hybrids like FOXM1 mRNA and its antisense transcript AS-FOXM1 (Zhang et al., 2017). Although changes in m^{6}A stoichiometry are subtle, the role of ALKBH5 in m^{6}A regulation is critical for specific biological processes.

2.3 m^{6}A "reader" proteins

The discovery of "writers" and "erasers" pioneered advancement in understanding RNA metabolism regulation. Subsequently, identification of m^{6}A binding proteins, known as "reader" proteins including YT521-B homology (YTH) domain proteins like YTHDF1 (Wang et al., 2015b), YTHDF2 (Wang et al., 2014a), YTHDF3 (Li et al., 2017a; Shi et al., 2017), YTHDC1, and YTHDC2 as well as hnRNPs (Alarcón, Goodarzi, et al., 2015a; Liu et al., 2015; 2017) and IGF2BP1-3 (Huang et al., 2018; Zhou and Pan, 2018a) significantly expanded our knowledge (Stoilov et al., 2002; Theler et al., 2014). The ability of "readers" to specifically recognize m^{6}A-modified RNA highlights their importance as key regulators in cellular biology.

2.3.1 DF family proteins

The DF family proteins are involved in cytosolic mRNA regulation, but their specific functions remain debated due to conflicting study results. DF2 is associated with mRNA decay by mediating the instability of m^{6}A containing mRNAs, with its depletion increasing half-lives of mRNAs through transient P-body interactions (Wang X. et al., 2014). Despite having similar binding sites and RNA preferences (Patil et al., 2016), studies have shown that DF1 promotes translation by engaging with DF3, eIF3, and various other initiation factors, without significantly affecting mRNA stability (Li H.-B. et al., 2017; Shi et al., 2017; Wang et al., 2015b). More recent research suggests that all DF proteins may share similar functions, including promoting mRNA degradation and deadenylation (Du et al., 2016). This idea is further supported by studies on Zika and HIV viruses, where DF proteins caused the degradation of virus-encoded m^{6}A transcripts (Gokhale et al., 2016a; Lichinchi et al., 2016a; Tirumuru et al., 2016a)

highlighting their functional redundancy and a broad impact on RNA stability and translation regulation.

2.3.2 DC family proteins

DC1, originally recognized as a nuclear splicing regulator, uses its YTH domain to bind m^{6}A-modified RNA and control alternative splicing (Xiao et al., 2016; Zhang et al., 2010). It also mediates an epigenetic role in gene silencing on the X chromosome through the action of noncoding RNA XIST, which relies on m^{6}A sites (Patil et al., 2016). Whereas, the function of DC2 (cytosolic) is less understood but includes enhancing the translation of hypoxia-inducible factor-1 α (HIF1α) mRNA, and degradation (Tanabe et al., 2016). It is not yet known if these roles involve m^{6}A recognition.

2.3.3 Heterogenous nuclear RNPs (hnRNPs)

Another class of m^{6}A readers includes HNRNPC (Liu et al., 2015), HNRNPG (Liu et al., 2017), and HNRNPA2B1 (Alarcón, Goodarzi, et al., 2015b) which recognizes and binds to m^{6}A-modified RNA through a "m^{6}A switch" mechanism. This process involves m^{6}A-induced structural changes in the stem-loop structure which weakens the base pairing within the m^{6}A consensus sequence, exposing RNA binding motifs for these enzymes (Kierzek and Kierzek, 2003; Liu et al., 2015). HNRNPC interacts with the newly accessible uridine track, while HNRNPG binds to purine-rich regions. Knock-out study of HNRNPC suggests that it plays a significant role in maintaining stability and alternative splicing of target RNA while, HNRNPG also contributes to the formation of cellular granules, essential for processing and localization of RNA (Liu et al., 2015; Liu et al., 2017). The role of HNRNPA2B1 is debated as it binds through the m^{6}A "switch mechanism"[57] but, also involved in pri-miRNA maturation by interacting with DGCR8 protein complex, highlighting its dual function (Alarcón, Goodarzi, et al., 2015b; Alarcón, Lee, et al., 2015).

2.3.4 IGF2BP1-3

Insulin-like growth factor 2 mRNA binding proteins 1, 2, and 3 (IGF2BP1–3) are a group of m^{6}A reader proteins that bind to the methylated mRNA through their KH (K Homology) domain, rather than typical YTH domain found in other m^{6}A readers (Huang et al., 2018). IGF2BP1-3 has a role in stabilizing the m^{6}A-modified mRNA, preventing degradation, and controlling gene expression. These proteins also play a significant role in cancer by enhancing the expression of oncogenic mRNA like MYC supporting the growth and survival of cancer cells (Huang et al., 2018; Zhou and Pan, 2018b). In upcoming sections, we discussed and highlighted the importance of m^{6}A methylation in infectious diseases.

3 m^{6}A methylation in infectious diseases

Infectious diseases are the major global health challenge causing approximately 13 million deaths every year (Gray and Sharara, 2022; Zumla, 2010). A range of harmful microorganisms including viruses, bacteria, parasites, and fungi are responsible for causing these ailments. Their mode of transmission can be airborne, waterborne, vector-borne, or via contaminated food and direct contact (Drexler and Institute of Medicine (US), 2010). Ranging from the Ebola epidemic to the recent COVID pandemic, infectious diseases have become a critical global concern.

In recent years, the involvement of m^{6}A in infectious diseases has garnered significant attention. Several breakthroughs in infectious disease pathogenesis have highlighted the significance of m^{6}A methylation in the interplay between host and pathogen, modulating the lifecycle and pathogenicity of infectious agents, thus emerging as a key player revealing novel therapeutic targets.

3.1 Viral infections

Apart from the presence of m^{6}A in cellular mRNA, its presence was also discovered in viral transcripts about half a century ago in 1985 (Lavi and Shatkin, 1975a), which opened new chapters in the field of molecular biology. Simian virus 40 (SV40) is one of the first viruses in which m^{6}A has been detected yielding almost 75% of the radioactivity (Lavi and Shatkin, 1975a). Subsequently, many more viral RNAs have been identified that contain m^{6}A methylation, including Rous Sarcoma virus (Kane and Beemon, 1985), influenza virus (Krug et al., 1976), herpes simplex virus (Moss et al., 1977), and many other viral families. Numerous studies have documented the effect of m^{6}A upregulation and deletion on viral replication, life cycle, and expression (summarized in Figure 1).

3.1.1 m^{6}A in HIV-1

The Human immunodeficiency virus type 1 (HIV-1), a member of the Retroviridae family, involves an enveloped, positive-sense, single-stranded RNA virus which is a primary causative agent of acquired immunodeficiency syndrome (AIDS) (Humans, 2012). The first study to report the presence of m^{6}A modification in HIV-1 RNA was conducted by Lichinchi et al. (2016). They showed that there is approximately a 30% increase in m^{6}A levels, reported in cellular poly(A) RNAs that were infected with HIV-1. Its topological analysis identified 14 m^{6}A peaks in both coding and non-coding sequences (Lichinchi, Gao, et al., 2016b). These results suggest that viral infections significantly increase the m^{6}A levels in both viral and host cell RNA (Lichinchi, Gao, et al., 2016b). However, the exact demonstration of this regulation was still lacking. To gain insight, a study conducted by Tirumuru and Wu (2019), claimed that the HIV-1 envelope proteins are responsible for the m^{6}A upregulation in CD4$^+$ T-cells even without the virus actively replicating, suggesting that the presence of virus alone triggers the rise of m^{6}A levels. They found a significant ~3-7-fold increase in m^{6}A levels upon infection with recombinant HIV-1 gp120 (Tirumuru and Wu, 2019).

To comprehend the impact of m^{6}A machinery, studies have utilized gain and loss of function strategies to observe their corresponding effects. The knockdown of m^{6}A writers, i.e., METTL3 or METTL14 resulted in reduced replication of the viral genome, as compared to control cells. Moreover, the concurrent depletion of both enzymes resulted in enhanced hindrance in viral replication (Lichinchi, Gao, et al., 2016b). Whereas, depleting the eraser enzyme ALKBH5 exhibited an increase in the same. Ultimately their findings demonstrated that both writers and erasers significantly affect the HIV-1 replication machinery (Lichinchi, Gao, et al., 2016b; Tirumuru et al., 2016b).

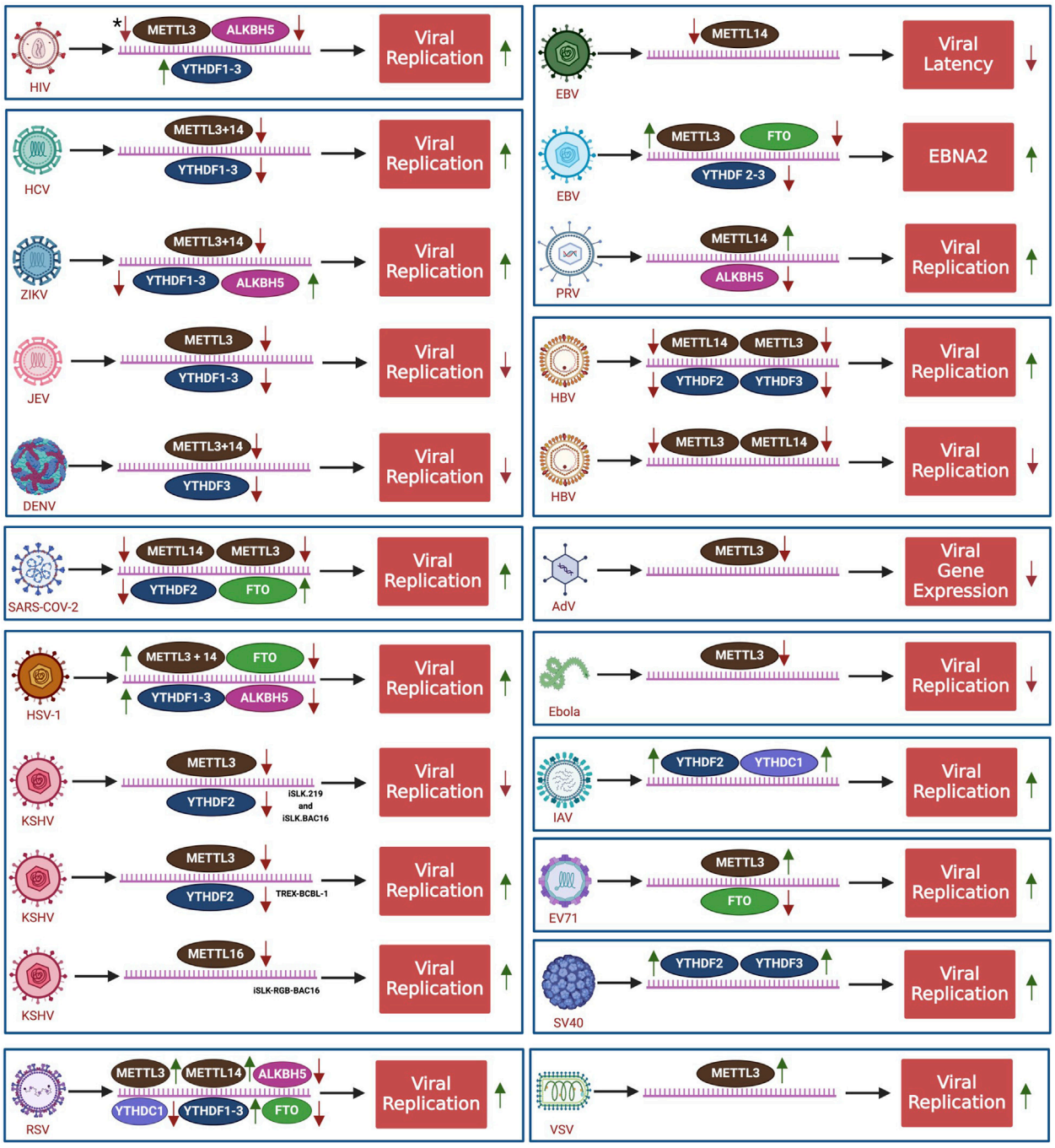

FIGURE 1
m^{6}A Methylation in Viral Infection: The figure illustrates the role of m^{6}A modification machinery components in modulating viral replication, protein expression, and latency across a variety of viruses. Each virus is associated with different m^{6}A writers (METTL3, METTL14, METTL16), erasers (FTO, ALKBH5), and readers (YTHDF1-3, YTHDC1), which can either promote or inhibit viral replication. Green (↑) arrows indicate the upregulation and red (↓) arrows indicate the downregulation of m^{6}A machinery. Each box represents viruses belonging to one family. *In HIV-1 infection knockout study on METTL3 showed reduced viral replication. Figure Created in BioRender, https://BioRender.com/n85v091

Furthermore, a recent study reported that some small molecules activate the methyltransferase activity of METTL3/METTL14/WTAP complexes which also leads to an increase in m^{6}A levels on both HIV-1 and host RNAs (Selberg et al., 2019; 2021). In 2016 two studies on m^{6}A readers presented contradictory findings. Study conducted by Tirumuru et al. found that depletion of YTHDF proteins increased HIV-1 infection, while upregulation decreased it. Thus, YTHDF1-3 proteins function as negative regulators, suppressing the HIV-1 infection after viral entry by interfering with reverse transcription (Tirumuru et al., 2016b). Contrarily, a study by Kennedy et al. demonstrated that the silencing of YTHDF significantly reduced and overexpression boosted HIV-1 RNA expression and viral replication. Thus dedicating YTHDF proteins, especially YTHDF2 as positive regulators (Kennedy

et al., 2016). This disparity in results might be due to methodological differences. However, the findings of other studies suggest a conflict with Tirumuru et al.'s statements and show that virions get degraded by viral protease and hence they cannot interfere with reverse transcription (Jurczyszak et al., 2020). Thus YTHDF proteins are considered to have a promoting effect on HIV-1 RNA expression (Jurczyszak et al., 2020; Kennedy et al., 2016; Lichinchi, Gao, et al., 2016b; Tsai et al., 2021).

3.1.2 m^{6}A in Flaviviridae

The members Flaviviridae family involve enveloped, positive-sense, ssRNA viruses that impact both human and animal life (Holbrook, 2017). This family of vector-borne viruses includes a variety of members (Holbrook, 2017), notably, the presence of m^{6}A methylation and its modulation has been identified in viruses including zika virus (ZIKV), dengue virus (DENV), yellow fever virus (YFV), hepatitis C virus (HCV), and japanese encephalitis virus (JEV) (Gokhale et al., 2016b; Yao et al., 2024).

Gokhale et al. (2016a), revealed an inhibitory effect on HCV production and replication (Gokhale et al., 2016b; Kim and Siddiqui, 2021). That means, the knockdown of MTases (METTL3+METTL14) increases the viral production while depletion of FTO decreased their levels, but no significant effect of ALKBH5 was found on the viral titer (Gokhale et al., 2016b). The impact of YTHDF1-3 proteins was found to increase HCV production on depletion[16].

A further study by Lichinchi et al. (2016) (Lichinchi, Zhao, et al., 2016) reported the same negative regulatory effect of m^{6}A methylation in ZIKV infection, as seen in HCV. Its topology showed 12 m^{6}A peaks in the ZIKV genome. The knockdown of methylases (METTL3+METTL14) and demethylases (ALKBH5) resulted in increased and decreased viral titer respectively, and showed opposite effects when over-expressed. Likewise, silencing YTHDF1-3 led to increased viral replication and expression, with YTHDF2 showing the greatest effect (Lichinchi, Zhao, et al., 2016). A recent exploration of the JEV exemplified a somewhat opposite effect of m^{6}A in its infection. The study claims that m^{6}A methylation has a positive regulatory role in JEV infection (Yao et al., 2024), which is different from the rest of the family members. They identified five m^{6}A peaks in the JEV RNA and upon infection attained more peaks. The METTL3, YTHDF1-3 silencing showed decreased JEV replication and expression. Whereas no significant effect was seen when writers and readers were overexpressed (Yao et al., 2024).

Furthermore, the relationship between m^{6}A methylation and DENV has also been investigated in mosquito (*Aedes aegypti*) cells (Dai et al., 2022) with a positive regulatory role in DENV infection by modulating writers and readers. The depletion of METTL3 and METTL14 in DENV-infected cells showed a substantial decrease (about ~three to four folds) in DENV RNA levels. A similar depletion of YTHDF3 caused decreased DENV production (Dai et al., 2022).

3.1.3 m^{6}A in SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the primary causative agent of the COVID-19 pandemic, has had unprecedented global impact. It is a member of the Coronaviridae family and *Betacoronavirus* genera (Liu P. et al., 2021), which is characterized by enveloped, positive-sense single-stranded RNA viruses (Wu et al., 2020; Zhou et al., 2020). m^{6}A profiling of SARS-CoV-2 has confirmed the presence of m^{6}A modifications in the viral genome (Becker et al., 2024; Liu et al., 2021). A study conducted by Zhang T. et al. (2021) identified 13 m^{6}A peaks in cells infected with SARS-CoV-2 (Zhang et al., 2021a). Additionally, research by Liu et al. (2021) concluded that SARS RNA gets methylated progressively during infection in host cells (Liu et al., 2021).

The interaction between m^{6}A-related proteins and SARS-CoV-2 infection has been widely investigated. Research led by Liu and co-workers found that viral infection caused increased m^{6}A methylation levels in both viral and host RNA (Liu C. et al., 2022). The knockdown of METTL3, METTL14, and YTHDF2 followed by SARS-CoV-2 infection resulted in increased viral replication and propagation. However, on ALKBH5 depletion, decreased viral replication was observed. Thus, concluding that m^{6}A methylation controlled by the host's cellular machinery has a negative regulatory role in SARS infection (Liu et al., 2021).

Augmenting the above results, a study by Zhang and co-workers (2021) found that overexpression of METTL3 decreases viral replication while FTO promotes it (Zhang et al., 2021b). Moreover, simultaneous knockdown of YTHDF1-3 significantly reduced positive cells by 72% (Burgess et al., 2021) suggesting that the m^{6}A readers contribute to viral replication and could be a promising target for antiviral drug development (Burgess et al., 2021; Liu et al., 2021).

3.1.4 m^{6}A in Herpesviridae

The herpesviruses possess a linear double-stranded DNA (dsDNA) genome (Feng et al., 2022b), which are characterized by their remarkable ability to establish lifelong infections and their biphasic life cycle, transitioning between both lytic and latent phases (Röder et al., 2022; Tan et al., 2018). Researchers have performed transcriptome-wide mapping of the m^{6}A methylation and identified its presence in Herpes simplex virus (HSV) (Moss et al., 1977), Kaposi's associated herpesvirus (KSHV) (Tan et al., 2018), Epstein-Barr virus (EBV) (Lang et al., 2019) and more recently in Pseudorabies virus (PRV) (Yu et al., 2023) in both lytic and latent transcripts.

Although the identification of m^{6}A in HSV-1 was done in 1977 (Moss et al., 1977), its role in antiviral innate response of the host did not get much attention. However, in recent years, m^{6}A modification was found to augment HSV-1 replication and infection (Feng et al., 2022b; Xu et al., 2023), while inhibiting m^{6}A by 3-deazaadenosine (DAA), a methylation inhibitor, blocked the viral reproduction (Z. Feng et al., 2022b). Similarly, in HeLa and human rhabdomyosarcoma (RD) cells, enhanced viral infection resulted in increased expression of METTL3, METTL14, and YTHDF1-3 in an early stage of infection whereas decreased the FTO and ALKBH5 expression (Feng et al., 2022b). Knockdown assay of writers and readers suppressed the viral replication and reproduction (Feng et al., 2022b; Xu et al., 2023).

The KSHV has developed a way to hijack the m^{6}A machinery of the host to enhance the lytic replication, thus indicating the crucial role of m^{6}A in regulating gene expression during lytic phase of viral life cycle (Ye et al., 2017). The m^{6}A reader, YTHDC1 along with SRSF3 and SRSF10 (serine/arginine-rich splicing factor) regulates

the splicing process on ORF50 pre-mRNA, which is highly involved in the viral gene expression and successful lytic phase (Ye et al., 2017). Silencing METTL3 and YTHDF2 in the KSHV-infected iSLK.219 (recombinant KSHV.219) and iSLK.BAC16 (rKSHV Bacterial artificial chromosome 16) cell lines show reduced levels of viral lytic activator ORF50 and impaired new virions production, respectively. However, these results showed disparity when cell type was changed. In TREX-BCBL-1 cell lines (B-cell), the knockdown of METTL3 and YTHDF2 had an opposite effect with increased ORF50 levels. Thus, signifying that m^{6}A regulation in KSHV infection is cell-type-specific (Hesser et al., 2018). Depletion of the other m^{6}A writer METTL16 in iSLK-RGB-BAC16 cells enhanced the KSHV lytic replication by promoting viral gene expression. That means, in a reduced scenario virus switches from a latent state to a lytic state. These results highlight the vital role of METTL16 in inhibiting the KSHV lytic replication (Zhang et al., 2023).

Recent studies have uncovered significant involvement of m^{6}A in EBV infection and its associated oncogenicity (Lang et al., 2019). The m^{6}A modification has been documented to play a dual role by promoting latency and suppressing lytic gene expression. METTL14 plays a crucial role in maintaining EBV latency, as higher METTL14 levels correlate with latent phase stability. Reducing METTL14 expression disrupts latency and promotes lytic gene expression (Lang et al., 2019). METTL3 enhances the expression of EBV nuclear antigen 2 (EBNA2) (a transcriptional activator) in the Raji cell, thus promoting its stability and translation. Depleting METTL3, decreased the expression of EBNA2. Moreover, the knockdown of FTO resulted in increased gene expression of EBNA2. The impact of m^{6}A readers on EBNA2 expression varied significantly. When YTHDF1 was reduced, EBNA2 levels dropped considerably, whereas reducing YTHDF2&3 led to increased expression levels (Zheng et al., 2021).

Another member of the Herpesvirus family, PRV is primarily known to infect porcine, but recent cases have shown to cause encephalitis in humans (Liu et al., 2021b). Yu et al. (2023) revealed a positive regulatory effect of m^{6}A in PK15 cells (porcine kidney epithelial cells) with increased m^{6}A levels during the infection. The knockdown of METTL3 and METTL14 resulted in decreased PRV replication, with METTL14 having more impact. Conversely, overexpression of METTL14 resulted in increased viral replication. Additionally, knockdown of ALKBH5 showed increased viral replication whereas FTO showed no significant effect. m^{6}A readers also endorsed viral replication (Yu et al., 2023).

3.1.5 m^{6}A in HBV

Hepatitis B virus (HBV), a member of Hepadnaviridae family, contains a double-stranded circular DNA and is a major human pathogen that is responsible for chronic liver diseases and capable of developing hepatocellular carcinoma (HCC) (Kim B. et al., 2020; Yang et al., 2023). HBV has been identified to contain m^{6}A modifications that regulate the viral life cycle (Imam et al., 2018). As previously discussed, m^{6}A modification occurs at specific consensus motifs, called "DRACH" sites. However, transcriptome-wide mapping of m^{6}A on HBV RNAs revealed that these consensus motifs are located within the epsilon (ε) stem-loop at both 5′ and 3′ terminus, and have dual effects (Imam et al., 2018). Methylation at the 5′ terminus is beneficial for the reverse transcription of pgRNA (pregenomic RNA) whereas methylation at 3′ end obstructs the RNA stability and thus is more prone to degradation. Substituting adenosine by cytosine at these motifs resulted in disrupted methylation, which led to decreased efficiency of reverse transcription and production of viral proteins (Imam et al., 2018).

Moreover, both m^{6}A methyltransferases and readers have been found to have a negative regulatory role in HBV protein expression. Depletion of METTL3, METTL14, YTHDF2, or YTHDF3 in HBV-infected cells showed increased viral protein (HBs and HBc) expression. However, the knockdown of erasers, FTO, and ALKBH5 had opposite effects and resulted in decreased expression (Imam et al., 2018). FTO suppression also resulted in the inhibition of HCC cell proliferation (Li et al., 2019b). O-GlcNAcylation (O-linked β-N-acetylglucosamine modification) of YTHDF2 is found significantly elevated in the HBV-infected cells which is responsible for the progression of hepatocellular carcinoma (Yang et al., 2023).

A recent study has uncovered the mechanism by which viruses evade the host's innate immune system using m^{6}A modification. Retinoic acid-inducible gene I (RIG-I) is a crucial detector of the viral RNA, as it provokes the production of type 1 interferon (IFN 1) and activates the innate immune response in the host cells. The study revealed that the presence of m^{6}A can regulate and impair the ability of RIG-I to recognize the viral RNA by masking the methylated RNA and eventually hindering the RIG-I signalling due to increased binding of YTHDF2. Silencing the METTL3 and METTL14 activated the innate immune response after the robust detection of the viral RNA by RIG-1 (Kim B. et al., 2020). This strategy can be exploited to develop a potent antiviral vaccine, wherein depleting the m^{6}A in viral RNA will promote enhanced immune recognition and trigger a protective response against viral infections.

3.1.6 m^{6}A in Adenovirus

Adenoviruses (AdV) belong to the Adenoviridae family that have non-enveloped double-stranded DNA genome (Henquell et al., 2009). It causes various diseases ranging from the common cold, conjunctivitis, respiratory infections, and gastrointestinal illnesses (Hajikhezri et al., 2023; Lu and Erdman, 2006). Identification of m^{6}A in adenoviral transcripts dates back to the 1970s which revealed its presence in both viral and cellular mRNAs (Sommer et al., 1976). In 2020, Price et al. utilized a combination of meRIP-seq and direct RNA long-read sequencing and identified m^{6}A sites in both early and late adenoviral genes, as well as in host cellular transcripts (Price et al., 2020). They found unaltered levels of METTL3, METTL14, WTAP, YTHDC1, YTHDF1 and YTHDF2. Conversely, they observed a modest increase in FTO and ALKBH5. Depleting METTL3, negatively affected the splicing efficiency of adenoviral transcripts and thus impacted viral expression in late genes, whereas early genes remain relatively less affected (Price et al., 2020). This implies that the loss of METTL3 has a greater effect during the later stages of the viral life cycle and can be considered as a potent therapeutic target to control viral replication.

3.1.7 m^{6}A in Ebola Virus

Ebola virus (EBOV) from the Filoviridae family contains a non-segmented, ssRNA genome and is reported to bear m^{6}A. They are

responsible for causing haemorrhagic fever in both humans and non-human primates (Martin et al., 2018; Wendt et al., 2023).The robust overexpression of METTL3 mildly inhibits viral processes whereas the knockdown of METTL3 reduced the viral RNA synthesis and protein expression. Other viruses that cause haemorrhagic fever, including Junín virus (JUNV) and Crimean-Congo haemorrhagic fever virus (CCHFV), are also influenced by METTL3, which regulates their transcription and protein expression (Wendt et al., 2023).

3.1.8 m^{6}A in Influenza A Virus

Influenza A virus (IAV), belonging to the family Orthomyxoviridae (Zhu et al., 2023) is unique among RNA viruses for having m^{6}A modifications in their complementary RNA (cRNA). The cRNA is a complimentary copy of viral RNA (vRNA) different from the non-methylated host mRNA. This modification in cRNA of IAV is likely to be mediated by the host nuclear enzymes, thus suggesting a relationship between viral replication and host cellular machinery (Krug et al., 1976). The m^{6}A plays a positive regulatory role, when METTL3 was depleted, it reduced the gene expression and virion production. Conversely, overexpressing the reader YTHDF2 enhanced virion production and also promoted the spread of viral plaques. Interestingly, overexpression of other reader proteins, YTHDF1 and YTHDF3, does not significantly impact viral replication (Courtney et al., 2017). Additionally, YTHDC1 levels were elevated during IAV infection and its silencing repressed the viral replication (Zhu et al., 2023).

3.1.9 m^{6}A in Chikungunya virus

The mosquito-borne Chikungunya virus (CHIKV) is a positive sense, ssRNA virus, belonging to the Togaviridae family, responsible for chikungunya disease characterized by high fever and severe joint pain (Jungfleisch et al., 2022; Kim et al., 2020a). The identification of m^{6}A modification in CHIKV was done by (Kim et al., 2020a), using a novel technique named viral cross-linking and solid phase purification (VIR-CLASP) along with mass spectrometry to explore the relationships between host and viral machinery. These methods indicated the m^{6}A presence and revealed the interaction between YTH-domain proteins and the CHIKV genome. The overexpression of YTHDF1 inhibited the viral replication whereas DF2 promoted it, with DF3 having a marginal influence on the replication (Kim et al., 2020a). However, another study by Baquero-Perez et al. (2024) challenges these findings and shows that the m^{6}A methylation did not affect the replication of CHIKV, using LC-MS/MS, SELECT, m^{6}A-seq, and nanopore sequencing. Moreover, the knockdown of writer or eraser did not impact the CHIKV infection (Baquero-Pérez et al., 2024). The authors also claimed the possibility of false positives achieved by methods like m^{6}A-seq in previous reports (Kim et al., 2020a), or its presence at very low stoichiometry. These contradictory findings raise questions about the presence and functionality of m^{6}A in cytoplasmic viruses like CHIKV. It also emphasizes the need for more robust methodological techniques.

3.1.10 m^{6}A in Enterovirus-71

Enterovirus type 71 (EV71), a positive-sense single-stranded RNA virus belonging to the Picornaviridae family (Hao et al., 2019), is majorly accountable for hand-foot and mouth disease (HFMD) in children (Xiao et al., 2021; Zhu et al., 2021). During EV71 infection, m^{6}A methylation was found to show a positive regulatory effect in the viral replication. Expression levels of METTL3, METTL14, YTHDF1-3, and YTHDC1 levels were enhanced while FTO levels were decreased. Depleting METTL3, YTHDF2, and DF3 showed reduced viral replication while FTO knockdown significantly promoted EV71 replication (Hao et al., 2019). In particular, METTL3 enhanced the translation of the EV71 open reading frame (ORF), promoting viral protein production and its replication. Deploying 3-deazaadenosine (3-DAA) which is an inhibitor of m^{6}A, affected the translation of ORF and eventually the replication. Notably, m^{6}A modification is also implicated in regulating EV71-induced apoptosis and autophagy. During EV71 infection the presence of METTL3 promotes autophagy, while its knockdown in Schwann cells reduces EV71-induced apoptosis which reduced viral titers (Xiao et al., 2021).

3.1.11 m^{6}A in Simian Virus 40

SV40 belongs to the Polyomaviridae family, which is considered a tumorigenic DNA virus. It has been associated with the development of brain and bone cancers, non-Hodgkin's lymphoma, and mesothelioma (Vilchez et al., 2003). The pioneering study that identified methylation in mRNA was conducted on Simian virus 40 (SV40) (Lavi and Shatkin, 1975b). Research conducted in the 1970s accurately mapped the internal methylation in SV40 mRNAs, revealing an average of three m^{6}A methylation, all located in the coding region (Canaani et al., 1979, p. 40). However, at that time the role of m^{6}A in regulating the viral life cycle was not broadly studied. A study directed by Finkel and Groner (1983), suggested the role of m^{6}A in the transport of mRNA from the nucleus to the cytoplasm and the facilitation of efficient production of late mRNAs (Finkel and Groner, 1983). The m^{6}A methylation in the SV40 infection has a positive regulatory role as the upregulation of the reader enhanced viral replication and its spread. Moreover, overexpressing YTHDF3 resulted in larger plaque formation than the control group. Conversely, when YTHDF2 and METTL3 were depleted it eventually inhibited the viral replication and spread (Tsai et al., 2018).

3.1.12 m^{6}A in Respiratory syncytial virus

Respiratory syncytial virus (RSV) belongs to the *Pneumoviridae* family, with a non-segmented negative sense (NNS) RNA genome, majorly responsible for respiratory tract infections in children and adults (Xue et al., 2019). Detection of m^{6}A in RSV RNA revealed the presence of 12 peaks, predominantly located in the 3′ end of the RNA (Csepany et al., 1990). m^{6}A peaks were majorly identified on the antigenomic RNA of N, P, G, and F genes, with the highest abundance on the G mRNA (Xue et al., 2019). The m^{6}A methylation in RSV is responsible for regulating viral replication, infection, and suppressing anti-viral host response (Picavet et al., 2024; Xue et al., 2019). The m^{6}A readers (YTHDF1-3) and writers (METTL3 and 14) have a positive regulatory role whereas erasers (FTO and ALKBH5) have a negative regulatory role in gene expression and replication. Thus, the overexpression of writers and readers and the knockdown of erasers can enhance severity of the disease (Xue et al., 2019). However, a recent study suggests that not all readers play a positive regulatory role. For instance, the nuclear reader YTHDC1 plays a

negative regulatory role by inhibiting viral entry (Picavet et al., 2024). Research led by Xue et al. (2021) highlights the implication of m^{6}A manipulation for developing attenuated vaccines by promoting robust innate and adaptive responses. Depleting the methyltransferase machinery and thus making an m^{6}A-deficient recombinant RSV RNA induces stronger type I interferon responses, ultimately boosting innate and adaptive immune responses. These mutants provided significant protection against the viral infection in cotton rats. Thus, targeting m^{6}A methylation provides a promising strategy to improve vaccine design against RSV (Xue et al., 2021).

3.1.13 m^{6}A in Vesicular Stomatitis Virus

Vesicular Stomatitis Virus (VSV), has a negative-sense, single-stranded RNA genome that belongs to the family Rhabdoviridae which primarily affects horses and cattle (Lu et al., 2021). The addition of m^{6}A to viral RNA reduced the formation of dsRNA and diminished the ability of host to trigger antiviral signalling pathways including RIG-I and melanoma differentiation-associated gene 5 (MDA5) for helping VSV to evade the detection. The m^{6}A writer METTL3 upregulation in VSV-infected HeLa cells resulted in enhanced viral mRNA production and replication by reducing the antiviral signalling. During VSV infection, METTL3 translocate to the cytoplasm and increases m^{6}A modification thus reducing the host's ability to recognize the virus which was further validated by knockout studies. These findings highlight a negative regulatory role of METTL3 for the host innate response during VSV infection (Qiu et al., 2021).

3.1.14 m^{6}A in Severe Fever with Thrombocytopenia Syndrome Virus

The negatively stranded RNA genome of Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV) of the family *Phenuiviridae*, also contains m^{6}A modifications (Wang et al., 2021b). The m^{6}A-seq analysis of SFTSV revealed the presence of approximately 11,520 m^{6}A residues in both infected and healthy patients. These were located in the coding sequence of 3′UTR. However, after infection, there was a significant reduction in the abundance of m^{6}A modifications on about 7,988 genes, suggesting the role of viral infection in the affecting methylation landscape. The FTO has been identified in greater abundance in infected patient samples (Wang et al., 2021b).

3.2 Bacterial infections

The m^{6}A modification was first identified in viral transcripts, leading to a deeper understanding of its role in viral biology. Recently, however, exploration of m^{6}A modifications in bacterial systems has begun to advance (summarized in Figure 2).

3.2.1 m^{6}A in *Helicobacter pylori*

Helicobacter pylori is a Gram-negative bacterium with a helical shape that is associated with chronic gastritis, peptic ulcers, intestinal metaplasia, and gastric cancer. The m^{6}A methylation on 3′UTR of Lectin-like Oxidized Low-Density Lipoprotein Receptor 1 (LOX-1), a key receptor in *H. pylori* adhesion, downregulates its expression which in turn reduces bacterial invasion and adhesion on the gastric epithelial cells (Zeng et al., 2024a). This aligns with a study by Cheng et al. (2023a) that highlights the role of FTO in the malignant transformation of gastric epithelial cells (GES-1) during chronic *H. pylori* infection. Acute infection with the CagA + strain of *H. pylori* leads to apoptosis in GES-1 cells, whereas chronic infection results in reduced apoptosis and promotion of tumorigenic traits, such as increased proliferation and invasiveness. This malignant transformation is due to the elevated FTO expression, which further modulates m^{6}A methylation on CD44 mRNA, a recognized marker of cancer stem cells. Silencing FTO reverses these transformations and reduces proliferation, migration, and tumorigenicity. Gastric cancer tissues showed higher levels of FTO and CD44, and elevated levels of FTO are associated with a poor prognosis in patients with gastric cancer. These studies highlight that FTO plays a pivotal role in *H. pylori* induced carcinogenesis, making FTO a potential therapeutic target for gastric cancer (Cheng et al., 2023a).

3.2.2 m^{6}A in *Escherichia coli*

Escherichia coli, a Gram-negative pathogen is known to affect both humans and animals globally causing public health issues such as dysentery and mastitis. Research has highlighted how m^{6}A modification influences the host cell response during *E. coli* infection. In intestinal porcine epithelial cells (IPEC-J2) when infected by *E. coli* F-18, the WTAP enhances the m^{6}A level on N-acetyl lactosaminide beta-1,6-N-acetylglucosaminyl-transferase (GCNT2) mRNA at the 3′UTR, later destabilized by YTHDF2. This limits the development of E. coli F-18 receptor by controlling the biosynthesis of glycosphingolipids mediated by GCNT2, which in turn enhance *E. coli* infection (Wu et al., 2022a). Similarly, studies on bovine mammary epithelial cells (MAC-T cells) demonstrated that the exposure to *E. coli* increased m^{6}A modification on LOC4191 (a lncRNA) to induce m^{6}A-mediated apoptosis that served as a defensive mechanism and limited the *E. coli* infection by removing compromised cells. However, upregulation of ALKBH5 demethylates the modification on LOC4191 RNA reducing apoptosis and potentially allowing *E. coli* to evade the host's defensive apoptotic response and enhances the infection (Xu et al., 2023a).

3.2.3 m^{6}A in *Mycobacterium tuberculosis*

Mycobacterium tuberculosis (MTB) is an anaerobic, rod-shaped, Gram-positive bacteria responsible for causing tuberculosis (TB) worldwide. Several studies by Zhang et al. examined no association between m^{6}A machinery components and their effect on pulmonary tuberculosis (PTB) susceptibility. However, their expression levels were relatively lower in PTB patients (Li et al., 2022a; Zhang et al., 2022b; Zhang et al., 2022c). But, recently Ma et al. (2024b) further explored the role of METTL14 in MTB infection. Upon MTB infection, p38 kinase get activated in macrophages which phosphorylates METTL14 at Thr72. Phosphorylated METTL14 undergoes liquid-liquid phase separation (LLPS) allowing it to form a complex with METTL3 more effectively. This complex of METTL3 and METTL14 methylates mRNA of the NAPDH oxidase 2 (Nox2) gene responsible for producing reactive oxygen species (ROS) for killing the MTB bacteria. However, an antigen EsxB (Rv3874), secreted by the bacteria, impairs the enzyme by deleting phosphorylation sites on

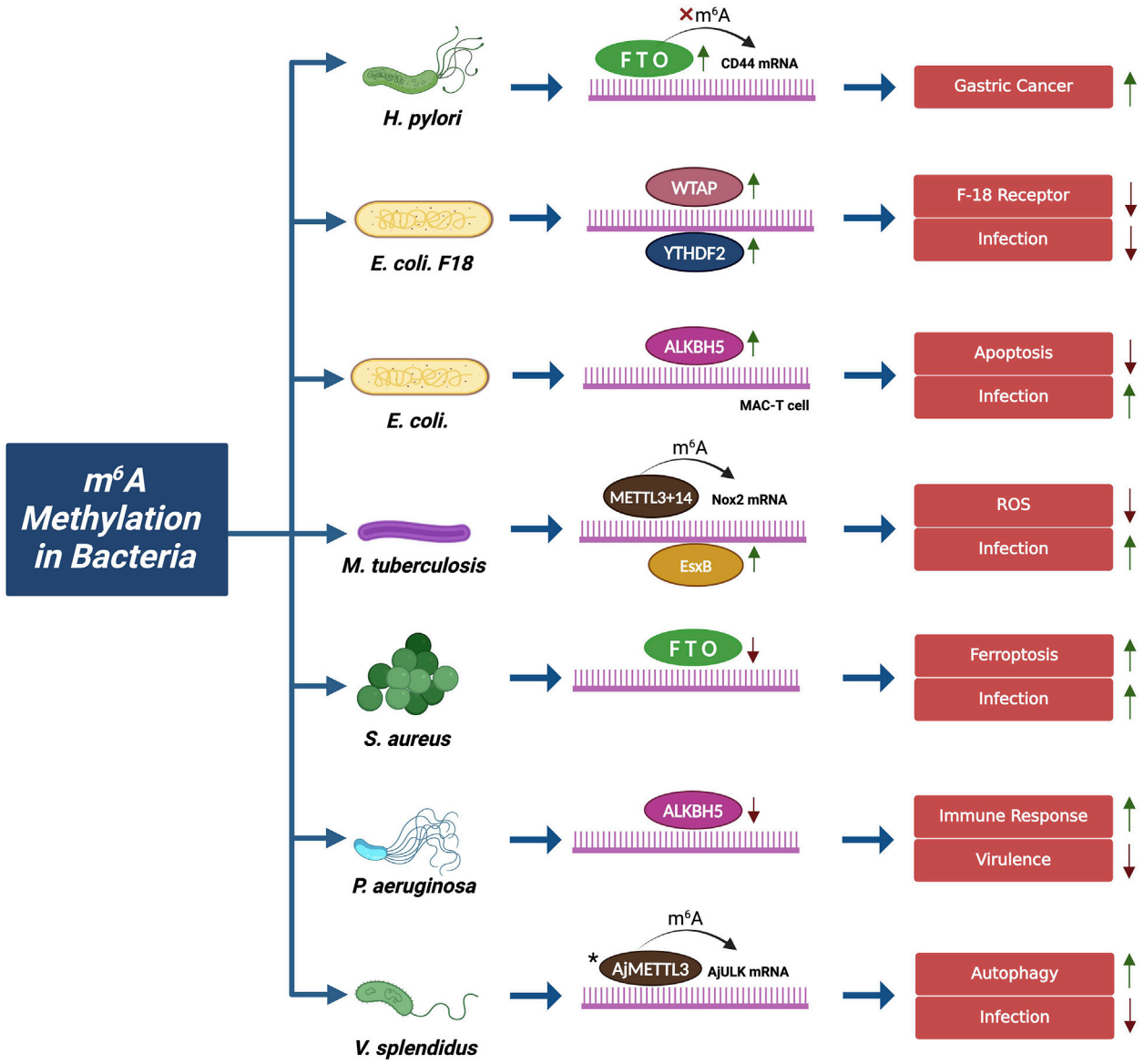

FIGURE 2
m⁶A Methylation in Bacterial Infection: The schematic illustrates the role of m⁶A modification machinery components in modulating various bacterial species and their effect on bacterial infection and pathogenesis. m⁶A proteins with green (↑) arrows show upregulation and red (↓) arrows show downregulation with their respective enhanced and repressed effects on infection. In *V. splendidus,* AjULK mRNA shows only its presence, with no upregulation and downregulation study. * Expression status is not studied (J. Liu et al., 2023). Figure Created in BioRender, https://BioRender.com/s09v404

METTL14, therefore, improving the survival of M. tuberculosis and enhancing the severity of the infection (Ma et al., 2024a).

3.2.4 m⁶A in *Staphylococcus aureus*

Staphylococcus aureus is another infectious bacterium, known to cause severe infections across species, leading to systemic inflammatory diseases such as sepsis. m⁶A modification plays a crucial role in *S. aureus*-induced sepsis by regulating gene expression through m⁶A-SNPs. A total of 15,720 m⁶A-cis-eQTLs (expression quantitative trait loci) and 381 m⁶A-trans-eQTLs were shown to be linked with sepsis, platelet degranulation, and various pathways involved in S. aureus infection. Apart from YTHDF3 (1 eQTL) and YTHDC2 (20 eQTLs), no other m⁶A regulator was found to be associated with sepsis (Sun et al., 2020). During *S. aureus* infection in bone marrow mesenchymal stem cells (BMSCs), elevated levels of m⁶A methylation due to reduced FTO were observed. This reduction in FTO leads to accumulation of Fe^{2+}, lipid peroxide, and malondialdehyde (MDA) which causes oxidative damage and ferroptosis in the cell, augmenting the bacterial infection. But, experimental upregulation of FTO protects the cell from ferroptosis by destabilizing MDM2-TLR4 (mouse double minute two homolog-Toll-like receptor 4) signalling and enhancing the expression of antioxidant proteins like solute carrier family seven members 11 (SLC7A11) and glutathione peroxidase 4 (GPX4), thereby protecting cells from ferroptosis-induced damage (Song et al., 2024). Another similar study showed that *S. aureus* reduces FTO expression in macrophages which might alter FoxO1/NF-kB signaling to modulate the immune regulation and thus

inflammation during infection (Liu et al., 2025). Hence, FTO can be used as potential therapeutic agent in managing *S. aureus* infections.

3.2.5 m^{6}A in other bacteria

Infection patterns of other significant pathogens are also influenced by this epitranscriptomic modification. For instance, in *Pseudomonas aeruginosa*, the m^{6}A modification is found on a distinct 5′-GCCAG-3′ motif compared to 5′-DRACH-3′ motif in the eukaryotes. The m^{6}A-modified mRNAs such as regulator of secondary metabolite gene expression YZ (RsmYZ) and rhamnosyl transferase A and B (rhlAB) were responsible for inducing virulence-like biofilm formation and antibiotic resistance during the infection (Deng et al., 2015). In *P. aeruginosa* infected RAW264.7 cells, ALKBH5 knockdown led to increased m^{6}A levels on numerous immune-related transcripts, resulting in the upregulation of 340 genes associated with immune responses hence, reduced the bacterial infection (Feng et al., 2022a). Similarly, in *Vibrio splendid* infection, m^{6}A mRNA methylation plays a crucial role in modulating autophagy in *Apostichopus japonicas*. The AjMETTL3-mediated modification on Unc-51-like kinase 1(AjULK) mRNA recruits AjYTHDF, which promotes AjULK expression through its interaction with translation elongation factor 1-alpha (AjEEF-1α). This mechanism enhances the autophagic response and reduces the *Vibrio splendidus* infection (Liu et al., 2023).

3.3 Parasitic infection

Besides viruses and bacteria, m^{6}A has become a significant regulatory mechanism in several parasitic protozoa essential for their development, survival, and infection cycle. Parasites, which rely on one or more hosts to complete their complex life cycle, must adapt to fluctuating environments and escape host immune responses. m^{6}A methylation enhances their stability by promoting effective gene expression in reaction to environmental stress. Several parasitic organisms, such as *Plasmodium* (Baumgarten et al., 2019), *Trypanosoma* (Serra et al., 2024a), *Toxoplasma* (Holmes et al., 2021a), and *Leishmania* (Zhang et al., 2022a), exhibit this epitranscriptomic modification which contributes to their pathogenicity and survival within the host system (summarized in Figure 3).

3.3.1 m^{6}A in *Plasmodium* sp.

Recent studies on *Plasmodium falciparum* have shown the role of m^{6}A mRNA methylation during blood-stage development. PfMT-A70, an orthologue of m^{6}A mRNA methyltransferase, is crucial for adding m^{6}A marks to mRNA, and silencing studies have identified its role in mRNA degradation and lower translational efficiency (Baumgarten et al., 2019). Notably, *P. falciparum* lacks demethylases but two putative m^{6}A binding YTH proteins (PfYTH.1 and PfYTH.2) were identified (Govindaraju et al., 2020a). Two similar studies by Govindaraju et al. and Sinha et al. characterized PfYTH.2, a key reader that binds specifically to m^{6}A-containing mRNA with the help of F98 residue in the aromatic amino acid cage (Govindaraju et al., 2020a; Sinha et al., 2021). The interaction of PfYTH.2 with eIF3 and poly(A)-binding proteins along with knock out study indicate its role as a host translational repressor in *P. falciparum*. By binding to the m^{6}A-modified mRNA, PfYTH.2 regulates the recruitment of the

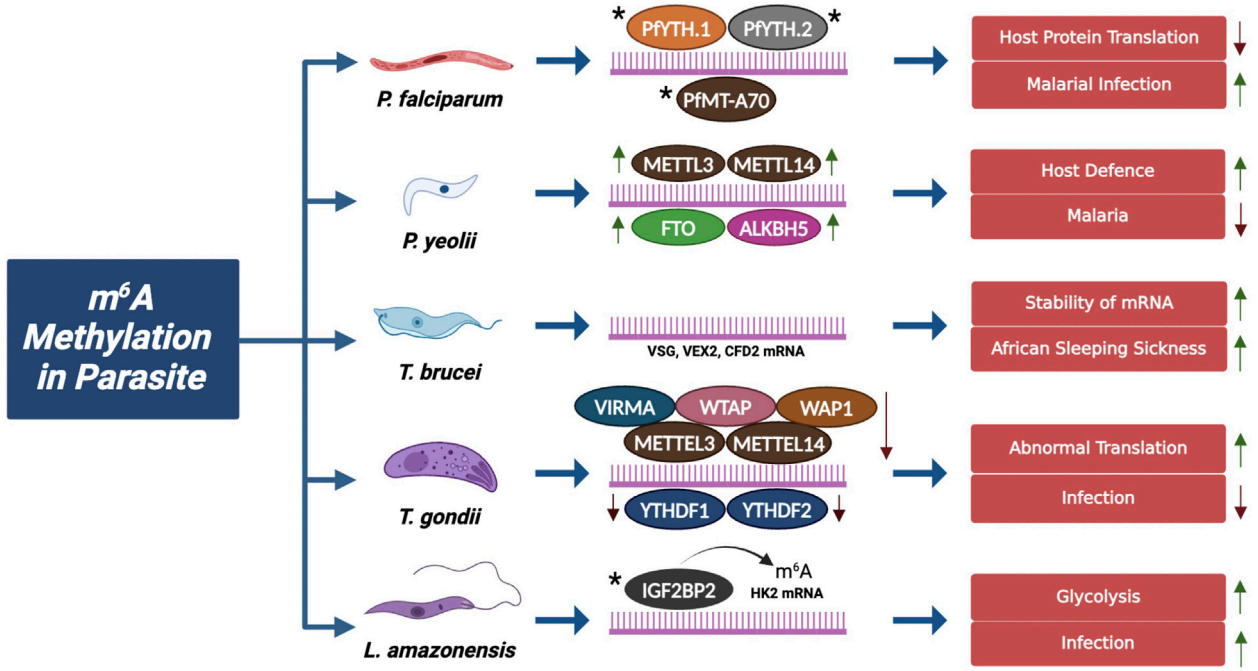

FIGURE 3
m^{6}A Methylation in Parasitic Infection: The schematic illustrates the role of m^{6}A modification machinery components in modulating various parasite species and their effect in facilitating their infection cycle. Green (↑) arrows indicate the upregulation with enhanced infection and red (↓) arrows indicate downregulation with suppressed infection. In *L. amazonensis* IGF2BP2 has no knockout studies, it only shows its presence. In *Trypanosoma brucei*, mRNAs do not comprise any m6A machinery. * Expression status is not studied (Liu et al., 2019; Serra et al., 2024a; Sinha et al., 2021). Figure Created in BioRender, https://BioRender.com/l22s429

translation initiation factor eIF3, thereby controlling the translation of mRNA necessary for the development and survival of the parasite. Knock-out study revealed that disrupting normal cellular localization of PfYTH.2 led to a notable increase in translational efficiency across target transcripts, suggesting that PfYTH.2 normally acts as a host translational repressor (Sinha et al., 2021). A different species of *Plasmodium*, *P. yoelii* was also used to study m^{6}A methylation during malarial infection. In infected mice, the m^{6}A/A ratio ranged from 0.52% to 0.55%, compared to 0.23% in non-infected mice. The study found that METTL3, METTL14, ALKBH5, and FTO were upregulated. m^{6}A modification on *Ifit2*, an interferon-stimulated gene, enhanced its expression in modulating host defence against malaria (Wang et al., 2022a).

3.3.2 m^{6}A in *Trypanosoma brucei*

Trypanosoma brucei is a single-celled parasite that causes African sleeping sickness in humans and nagana in cattle affecting a large region of tropical Africa. It is found in two stages-bloodstream form (BSF), inside the human host, and procyclic form (PCF) inside the vector, i.e., tsetse fly. Using the method of m^{6}A-CLIP, researchers found 355 m^{6}A peaks across 251 genes in PCF and 95 peaks across 51 genes in BSF (Liu et al., 2019). In the BSF stage of the parasite, 50% of the modification occurs on mRNA encoding for variant surface glycoprotein (VSG), crucial for survival within the human host. The m^{6}A methylation occurs on the poly (A) tail of the VGS transcript to enhance mRNA stability by preventing deadenylation (Viegas et al., 2022). Not only VGS but two important proteins, VSG-exclusion protein 2 (VEX2) and cyclin-like F-box 2 (CFB2), which regulate the gene expression of VGS were also found to be methylated (Serra et al., 2024a). However, the specific roles of m^{6}A "writers", "erasers", and "readers" have not been investigated, indicating a significant research gap in this field.

3.3.3 m^{6}A in *Toxoplasma gondii*

Another parasite responsible for causing food-borne illness and infection in immune-compromised patients is *T. gondii*. The infection cycle in *Toxoplasma gondii* is regulated by the m^{6}A "writer" complex consisting of METTL3, METTL14, WTAP, a novel writer-associated protein (WAP1), and an uncharacterized VIRMA but, lacks eraser proteins. The reader proteins, YTH1 and YTH2, bind with m^{6}A methylomes and help in the 3′end formation of mRNA by associating with the polyadenylation mechanism. A knockdown study of "writers" and "readers" showed that m^{6}A is crucial for proper termination of transcription; its absence leads to abnormal gene expression suppressing *T. gondii* infection (Holmes et al., 2021a).

3.3.4 m^{6}A in *Leishmania amazonensis*

Leishmania amazonensis is a protozoan parasite responsible for causing leishmaniasis, by invading and residing within the host immune cells such as macrophages. Similar to all other parasites, *L. amazonensis* utilizes m^{6}A methylation machinery to regulate gene expression for infection and survival within the host. Normally, macrophages are present in either the M1 state (antimicrobial activity by aiding T helper type 1 response) or the M2 state (anti-inflammatory and promote T helper type 2 response), but, in *Leishmania*-infected macrophages (LIMs) markers of both the states were expressed. This process is controlled by the m^{6}A "reader" protein IGF2BP2 which identifies and binds to m^{6}A-modified transcripts of the glycolytic enzyme hexokinase-2, which increases the stability of these transcripts. This stabilization leads to higher expression of glycolytic enzymes, enhancing glycolysis and providing necessary energy to the parasite, aiding the survival of the pathogen (Zhang et al., 2022a).

4 Therapeutic potential of the m^{6}A methylation in infection biology

Achieving the translation of mRNA *in vitro* for therapeutic applications took almost 2 decades as we have witnessed the development of mRNA vaccine against SARS-CoV-2 (Karikó, 2022; Sahin et al., 2014). Not only mRNA, drugs based on siRNA such as patisiran, inclisiran, gevosiran, and lumasiran and antisense oligonucleotides like golodisen were approved recently by FDA (Curreri et al., 2023).

Recently, the m^{6}A modification has been exploited for therapeutic purposes to cure or monitor the progression of metabolic diseases such as cardiovascular complications and various types of cancers (Qiu et al., 2023). More than 50 inhibitors have been studied to target m^{6}A methylation machinery, specifically writers METTL3/14, and erasers FTO and ALKBH5. These inhibitors include adenosine analogues, flavenoids such as quercetin and scutellarin, allosteric inhibitors, receptor agonists, and other natural compounds such as Rhein and radicicol, etc. along with amine derivatives like MU06 (Liao et al., 2022; Qiu et al., 2023; Wang et al., 2018; Yan et al., 2018; Yankova et al., 2021). Developing inhibitors against readers (YTH domain-containing proteins) is also of keen interest in regulating the functional consequences of m^{6}A modification. The YTH domain recognizes m^{6}A methylation and the organoselenium compound ebselen disrupts this recognition by interfering with RNA binding properties of YTHDF1-3 but not of YTHDC1 (Micaelli et al., 2022). Another study on the YTHDF1 reader showed that the deletion of YTHDF1 in hepatocellular carcinoma reduced the stemness and drug resistance against lenvatinib and sorafenib anti-cancer drugs. YTHDF1 enhances tumorigenesis by stabilizing m^{6}A methylated NOTCH1 mRNA (Zhang et al., 2024). Interestingly, the anti-cancer drugs either target m^{6}A methylation pathways or are used in combinatorial therapy with m^{6}A methylation targets were shown to be more effective in treating different cancers. For example; in non-small cell lung cancer and cervical cancer, targeting FTO and METTL14 with gefitinib and sorafenib treatments leads to improved tumor suppression respectively (Chen et al., 2022a; Li et al., 2024). The drug resistance against tyrosine kinase inhibitors can be improved by reducing the expression of m^{6}A eraser FTO (Yan et al., 2018). A detailed discussion on the types, purpose, and bedside clinical success is out of the scope for this review but we mentioned the future therapeutic directions particularly related to infectious diseases.

As discussed earlier, developing a vaccine against RSV is still challenging due to host-virus interactions which results in compromised adaptive and innate immune responses after RSV infection. Impairing with m^{6}A methylation either by knockdown of

METTL3 or using defective RNA (by removing putative m^{6}A sites) resulted in an activated interferon response pathway which enhanced innate immune response followed by enhanced T cell activation during adaptive response. This study can be implemented in either RNA-based vaccine production or designing m^{6}A defective viral particles to be used in attenuated viral vaccine production (Xue et al., 2021).

A similar study in HSV-1 infection identified the role of m^{6}A methylation machinery in facilitating strong viral replication and propagation at the early stage of the infection. HSV-1 upregulated the expression of METTL3/METTL14 and oppositely reduced the expression of FTO and ALKBH5 for the robust m^{6}A methylation of viral RNAs. Both depletion of m^{6}A methylation machinery components (METTL3 and YTHDF3) and inhibition of m^{6}A methylation by 3-deazaadenosine severely reduced viral replication and further spread, suggesting METTL3 and YTHDF3 mediated therapeutic avenues to be explored (Feng et al., 2022b).

Research on deadly SARS-CoV-2 and less virulent HCoV-OC43 identified that both viruses use m^{6}A methylation for their replication and propagation. SARS-CoV-2 significantly induces the nuclear localization of cytoplasmic METTL3 and YTHDF1-3 to enhance m^{6}A methylation of the viral RNAs, especially for enhanced production of nucleocapsid (N) protein. This study also highlights the importance of exploiting m^{6}A methylation therapeutic purpose to combat the SARS-CoV-2 infection (Burgess et al., 2021).

It would be interesting to note here that bacteria and viruses lack their own m^{6}A methylation machinery genes but parasites such as *P. falciparum* and *T. gondii* have their own m^{6}A methylation writers and readers. The *P. falciparum* writer PfMT-A70 is an orthologue to mammalian METTL3 but readers such as PfYTH1 and PfYTH2 are less similar to mammalian counterparts other than conserved YTH domain which is essential to identify methylated adenosine (Baumgarten et al., 2019; Govindaraju et al., 2020b). Unlike YTHDC1 which prefers guanine at −1 and cytosine at +1 position to bind m^{6}A, PfYTH2 is more permissible for the flanking sequences which is similar to YTHDF1-2 proteins. In case of *T. gondii*, YTH1 and YTH2 show homology with plant like reader protein known as polyadenylation specificity factors 30 (CPSF30, contains characteristic zinc finger domain) and are required for m^{6}A dependent 3′end processing on mRNA transcripts (Holmes et al., 2021a). Thus, selecting m^{6}A methylation genes for bacterial and viral infections for identifying therapeutic options is easier but future findings are absolute to wisely target parasitic m^{6}A machinery by identifying key similarities and differences in protein sequence and structures.

Overall, RNA therapeutics is a newly emerging field for designing new cost-effective, and personalized medicines. Currently, no therapeutic drugs specifically targeting the m^{6}A network have been approved for clinical use or are in preclinical trials. However, research in this area is promising, and several studies have highlighted the potential of m^{6}A modification as a therapeutic target for various diseases, particularly cancer. In this review, earlier we have mentioned such potent small-molecule inhibitors of m^{6}A machinery (Micaelli et al., 2022; Selberg et al., 2019; Yankova et al., 2021) that are highly feasible for clinical applications in infectious diseases. Technical advancements in next-generation sequencing play a crucial role in uncovering regulatory mechanisms governed by different types of RNAs and open limitless possibilities to add novel RNA-based drugs. The mRNA vaccine against SARS-CoV-2 exploited different RNA modifications such as pseudouridylation, m^{5}A, m^{1}A, etc. to stabilize mRNA and reduce immunogenicity (Granados-Riveron and Aquino-Jarquin, 2021). These modifications are highly understudied in infectious diseases, along with their interplay with m^{6}A methylation as well as with other epigenetic markers such as histone modifications and DNA methylation.

5 Discussion and conclusion

The methylation is catalyzed by a methyltransferase-like (METTL) family of proteins having S-adenosyl methionine (SAM) binding domain on DNA, RNA, and proteins, as their molecular substrates. A plethora of functions of different METTL proteins have been identified in cancer and stem cell biology. METTL3-METTL14 (act as heterodimer), METTL16, METTL4, METTL7A, and METTL5 all catalyze m^{6}A methylation on mRNA, rRNA, tRNA, miRNA, snRNA, snoRNA, lncRNA, and mitochondrial DNA (Tooley et al., 2023). As we have observed in above sections, HIV, HCV-1, PRV, IAV, EV71, SV40, RSV, VSV, and adenovirus increase the m^{6}A methylation either by activation of m^{6}A writers METTL3 and METTL14 or by increase in readers such as YTHDF1-3 or by modulation of erasers like ALKBH5 for their viral replication (Kennedy et al., 2016; Lichinchi, Gao, et al., 2016b; Selberg et al., 2021; Tirumuru et al., 2016b). Additionally, there are evidences that YTH reader proteins recruit RNA-binding proteins to influence infection in certain viruses. In HBV infection, YTHDF2 recruits 3′-5′ exonuclease Interferon-stimulated gene 20 (ISG20) and binds to the epsilon-stem loop structure on the viral RNA for its degradation (Imam et al., 2018; Liu et al., 2017). Whereas, in KSHV infection, YTHDC2 protects the cellular mRNA by interacting with the m^{6}A modified SOX resistance element in the Interleukin-6 (IL-6) transcript to prevent the degradation from the viral endoribonuclease ORF37 (SOX) (Macveigh-Fierro et al., 2022).

Oppositely, in HCV, ZIKA, SARS-CoV-2, HBV, and SFTSV infection, m^{6}A methylation has the reverse role as it reduces the viral replication. The silencing of METTL3 and METTL14 increased the viral production in contrast FTO deletion decreased the viral load (Gokhale et al., 2016b; Imam et al., 2018; Lichinchi et al., 2016; Liu et al., 2021; Wang et al., 2021b; Yao et al., 2024).

The role of METTL4, METTL7A, and METTL5 is not identified in any of the above-mentioned infections. Other family members such as METTL1 add methyl group on guanine, METTL6, METTL8, METTL17 on cytosine, and METTL19 on uracil on different types of RNA. Interestingly METTL3, METTL10, METTL11, METTL12, and METTL22 are also responsible for methyl group catalysis on various protein substrates (Tooley et al., 2023). The methylation specificity (m^{6}A, m^{5}C, m^{6}A.m., m^{7}G) and substrate identification (type of RNA) are still under investigation. Most pathogens usually inactivate, break, deceive, silence, or escape the innate and adaptive immune system pathways for their survival, proliferation, and spread. The role of m^{6}A methylation and other METTLs in infection biology has not been explored which is absolutely

needed to fill the gap of immune regulatory mechanisms. As shown in other diseases, m^{6}A methylation is involved in anti-tumor, anti-inflammatory, and anti-viral immunity. The m^{6}A writer METTL3, readers YTHDF1-3, and erasers FTO and ALKBH5 have been reported to regulate key immune pathways like macrophage polarization, dendritic cell activation, and antigen presentation (Li et al., 2017b; Ma et al., 2021b).

In bacterial infections a few cell line studies on m^{6}A methylation during *E. coli*, *M. tuberculosis*, *S. aureus*, *P. aeruginosa,* and *H. pylori* infections have identified specific regulatory roles either benefiting bacterial growth or inhibiting bacterial virulence. For example,; during *H. pylori* infection with gastric epithelial cells, m^{6}A methylation of LOX-1 and CD44 transcripts reduced the bacterial pathogenesis whereas the methylation enhances the tumorigenic properties of epithelial cells post *H. pylori* infection (Cheng et al., 2023b; Zeng et al., 2024b). Similarly, in *M. tuberculosis* pathogenesis, METTL14 phosphorylation is suppressed by bacteria to decrease ROS production thus supporting bacterial survival (Ma et al., 2024b). During *E. coli* F-18 infection in IPEC-J2 cells, m^{6}A methylation enhances the host response by increasing m^{6}A levels of GCNT2 which in turn limits infection (Wu et al., 2022b). Another study with MAC-T cells showed that *E. coli* infection increases m^{6}A modification on a long noncoding RNA, LOC4191 which enhances the cell apoptosis and thus reduces the severity of infection (Xu et al., 2023b). Additionally, YTHDF1 shows interaction with DEAD domain in the host factor DDX60 (RNA helicase) to bind with the m^{6}A-modified mRNA and increase translation of TRAF6 molecule involved in nuclear factor-κB (NF-κB) signalling enhancing innate immune response (Zong et al., 2021). In *S. aureus* infection, m^{6}A methylations of bacterial rRNA and host circRNA play a crucial role in regulating infection events such as inflammation and cell apoptosis (Xu et al., 2022).

m^{6}A methylation is extensively discussed for its application as potential biomarkers in various diseases such as diabetes, cardiovascular disease and cancer (Li et al., 2022b; Li et al., 2023; Liu et al., 2022a; Liu et al., 2022b; Tang et al., 2023). Though we have limited research in infectious diseases but very recently in human patient's datasets, four genes including YTHDF1, HNRNPC, LRPPRC, and ELAVL1 have been identified and suggested as biomarkers for *M. tuberculosis* infection. These results were experimentally validated using RT-PCR and the expression of all four genes was significantly lower in MTB infected patients compared to the healthy control (Ding et al., 2024). Similarly, another computational analysis in healthy and SARS-CoV-2-infected patients has identified 18 m^{6}A machinery regulators that were differentially expressed and reported that eight genes could be used for predicting COVID-19 infection. Among these, VIRMA, HNRNPA2B1, and RBM15B were shown to be protective factors whereas elevation of METTL3, RBM15, IGFBP3, FMR1 and ELAVL1 were associated with increased pathogenicity of the virus (Qing et al., 2022). The two m^{6}A readers HNRNPA2B1 and RBM15 were shown to be important for predicting the prognosis of hepatitis B virus mediated hepatocellular carcinoma (Fang and Chen, 2020). Though, the experimental validation and further efforts for clinical applications for these studies are still awaited.

The m^{6}A regulation is highly dynamic in parasitic infections. Apicomplexa parasites such as *P. falciparum* and *T. brucei* have their own m^{6}A machinery. The *Plasmodium* m^{6}A reader protein, PfYTH.2 interacts with eIF3 and poly(A)-binding proteins and reduces the host protein translation to promote parasite survival (Sinha et al., 2021). *P. yoelii* infection also increases m^{6}A methylation but this pathogen enhances the expression of host m^{6}A writers and easers. Now, this intrigues an interesting question that the increase in the writer's expression results in a 52% increase in the m^{6}A/A ratio which should be reduced after an increase in eraser expression. It is possible that *P. yoelli* might be directing easers in other pathways to support parasitic infection (Wang et al., 2022b).

During *T. gondii* infection m^{6}A methylation gets upregulated by its own writer complex having WAP1 as a novel component compared to other eukaryotes. Identifying similar novel components will help to understand the site and stimulus-specific regulation of m^{6}A methylation. Hypermethylation of RNA targets helps *T. gondii* in establishing the infection as the knockdown of m^{6}A machinery suppresses the pathogenesis (Holmes et al., 2021b; Serra et al., 2024b). *Leishmania* uses the reader protein IGF2BP2 to bind with hypermethylated transcripts such as hexokinase-2 two which in turn supports the parasite survival in the host macrophage (Wang et al., 2021a).

So far, no RNA based therapeutic drug targets have been identified in parasites. The absence of DNA methylation in certain parasites may suggest a dependence on RNA modifications like m^{6}A for gene regulation, but this area is unexplored to provide sufficient evidence to draw definitive conclusions.

Since 1928, infectious diseases have been efficiently treated with the help of antibiotics (Fleming, 1929). However, the widespread excessive use of antibiotics has led to antibiotic resistance in bacterial species, leading to severe health threats worldwide (Park et al., 2010). One of the major causes for resistance development is due to m^{6}A methylation on the bacterial 23S rRNA catalysed by Erm (erythromycin resistance methylase)-type rRNA methyltransferases on nucleotide A2058 (Weisblum, 1995; Graham and Weisblum, 1979; Stojković et al., 2016). This modification is present in *E. coli, S. aureus, Streptomyces* spp. *Bacillus* spp. etc., providing resistance towards macrolides, lincosamides, and streptogramin B (MLS) antibiotics (Weisblum, 1995; Graham and Weisblum, 1979; Sharkey et al., 2022; Svetlov et al., 2021). The basic mechanism involves the addition of two methyl groups on the N6 amine of A2058 by Erm methyltransferase leading to steric hindrance between MLS antibiotics and ribosome, rendering the antibiotics ineffective to inhibit translation of bacterial protein, immune evasion by preventing recognition by Toll-like receptors (TLRs) and contributing to bacterial fitness (Sharkey et al., 2022; Shields et al., 2024; Svetlov et al., 2021). Hence, understanding the molecular and structural basis of such resistance mechanisms is important for developing novel RNA based antimicrobial strategies.

Our keen observation on the role of m^{6}A methylation in infection biology leads us to conclude that every pathogen modulates m^{6}A methylation in their unique way thus suggesting the stimuli-specific regulatory mechanism. Some pathogens modulate the writer complex; the others modify either readers or easers. The complex interactome and reason behind this selection is unknown. This certainly warns extensive research to control deadly

infections and generate a healthy therapeutic armoury to overcome the exponentially increasing drug resistance.

Author contributions

NY: Conceptualization, Validation, Writing–original draft, Writing–review and editing. ReK: Conceptualization, Visualization, Writing–original draft, Writing–review and editing. SG: Software, Validation, Visualization, Writing–original draft, Writing–review and editing. RaK: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing.

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