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Interplay of RNA 2′-O-methylations with viral replication

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Highlights

- Viral RNA genomes are modified by epitranscriptomic marks, such as 2′-O-methylation.
- 2′-O-methylations are self-markers hijacked by viruses to avoid immune sensing.
- Modified viral RNA counteract restriction by interferon-stimulated genes.
- New insights suggest that 2′-O-methylations also impair viral replication.

Abstract

Viral RNAs are decorated by post-transcriptional modifications, including methylation of nucleotides. Methylations regulate biological functions linked to the sequence, structure, and protein interactome of RNA. Several RNA viruses were found to harbor 2′-O-methylations, affecting the ribose moiety of RNA. This mark was initially shown to target the first and second nucleotides of the 5′ end cap structure of mRNA. More recently, nucleotides within viral RNA were also reported to carry 2′-O-methylations. The consequences of such methylations are still puzzling since they were associated with both proviral and antiviral effects. Here, we focus on the mechanisms governing viral RNA 2′-O-methylation and we explore the possible roles of this epitranscriptomic modification for viral replication.

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Introduction

Epitranscriptomic modifications are co- or post-transcriptionally biochemical modifications of the nucleotides incorporated in RNA molecules. To date, more than a hundred possible nucleotide modifications are identified [1,2], and their importance in regulating the structure and function of many cellular RNAs has been established. RNA viruses are not spared from epitranscriptomic mark addition. As they represent a major threat on public health, the impact of such modifications on viral RNA (vRNA) is under investigation. However, the lack of sensitive methods to detect the presence of such modifications on vRNAs has delayed the discovery of their biological role. Recent technological developments have allowed the identification of a wide diversity of epitranscriptomic marks on vRNA [3]. Methylation of RNA nucleotides at different positions on the nucleobase or the ribose is an abundantly detected modification (reviewed in [4**]). Among them, N6-Methyladenosine (m6A), N5-Methylcytosine (m5C), N1-Methyladenosine (m1A) and 2′-O ribose methylation (Nm) are frequently observed (**Figure 1.A & 1.B**). Characterization of several of these modifications within vRNA has recently unveiled their key role for the replication of some viruses (see reviews [4**–6**]).

To date, the best characterized nucleotide modification is the m6A (**Figure 1.B**). This is due to its abundance in RNA, but also to the efficiency of m6A detection methods [7]. Another important epitranscriptomic modification is the methylation of the nucleotide ribose at the 2′-OH moiety (**Figure 1.B**), added by 2′-O-methyltransferases (2′-O-MTases). In contrast to m6A, Nm are stable RNA modifications. Nm are ubiquitous, on all types of RNA templates, and across Eukarya, Bacteria and Archaea. Nevertheless, the addition of Nm is finely regulated, notably during cellular stress [8]. Regarding eukaryotic cells, Nm decorate the mRNA 5′-cap structure which is an inverted N7-methylguanosine moiety linked to the first transcribed nucleotide (N1) through a 5′-5′ triphosphate bridge (N7mGpppN1 or cap-0 structure [9]). The RNA cap is added co-transcriptionally in the nucleus during RNA synthesis by RNA Pol II. It is subsequently methylated by cap methyltransferases, namely CMTR 1 and 2 in humans, which transfer a methyl group to the 2′-OH of the ribose of the first and second transcribed nucleotides, yielding cap-1 (N7mGpppNm) and cap-2 (N7mGpppNm-Nm) structures respectively [10].

Internal Nm sites have also been described for many RNA species. Internal Nm addition seems to take place co-transcriptionally in the nucleus, as demonstrated by the detection of Nm on the yeast 18S rRNA precursor before it leaves the RNA Pol I machinery [11], and even in introns within mammalian mRNA [12]. Nm are commonly catalyzed at base precision on rRNA by a ribonucleoprotein complex composed of a C/D box small nucleolar

RNA (snoRNA) which pairs with a specific RNA sequence, and proteins such as the nucleolar 2′-O-MTase called Fibrillarin (FBL). For instance, the snoRNA U104 mediates Nm on rRNA with FBL [13], but other 2′-O-MTases operate regardless of snoRNA, like FTSJ3 [14].

Quantitatively, human tRNA carries at least 3 Nm (reviewed in [4**]), while human rRNA contains not less than 106 Nm [15]. Furthermore, recent studies reveal that Nm affect about 0.5 to 1.4 % of mRNA content, including both cap and inner Nm sites [12,16]. Internal Am, Cm and Gm seem favored (more than 25% of all Nm sites each) compared to Um (about 10%), and it is likely that the coding sequence is less methylated than the 5′ and 3′ UTR region of mRNA [12,17**].

Once generated, Nm are proved to have numerous roles regarding the structure and function of RNA molecules. First, they are involved in critical molecular interactions supporting RNA secondary structure [18*–20] or stacking and rigidity [21]. Second, they can affect mRNA translation, as internal Nm on mRNA and rRNA respectively interfere with [16,22], or regulate translation [23,24]. Furthermore, Nm improve RNA stability when incorporated within the cap structure by limiting the activity of decapping enzymes like the decapping and exoribonuclease protein DXO [25], or at the 3′ end by preventing degradation by exonucleases [26*,27]. Recently, several studies revealed that Nm play a role as a self-marker (see below). Increased evidences demonstrate the importance of such epitranscriptomic marks, as dysregulations can cause diseases [28,29], or be studied as a marker of cancer heterogeneity [30**].

Today, an enhanced sensitivity for quantification and a mapping of Nm at base precision are reached, thanks to methods like ultra-high-performance liquid chromatography linked to tandem mass spectrometry (UPLC-MS/MS [31]), nanopore sequencing [32*], alkaline hydrolysis (RiboMethSeq [33,34]) and oxidation by periodate (Nm-seq [12]). These techniques overcome issues like low abundance of viral RNA species, and rare occurrence of Nm at certain positions.

While the molecular mechanisms governing Nm modifications on the different kinds of vRNA remain poorly described, many studies have evidenced that these marks are regularly found on vRNA, and modulate the success of viral infection by regulating replication and the antiviral innate immune response.

How RNA viruses ensure 2′-O-methylation of their genome

2′-O-methylation of the cap structure

The modification of viral genomic RNA (gRNA) or mRNA by the addition of a 5′ end cap structure and its subsequent N7- and 2′-O-methylation is one of the best characterized post-transcriptional modifications (reviews [35–37]) affecting positive-sense RNA. Briefly, the cap structure present at the 5′ end of RNA is adopted by many viruses infecting eukaryotes, as this modification is important for mRNA translation and stability. However, some viruses use alternative strategies to ensure their translation by using an Internal Ribosome Entry Site (IRES) that recruits the ribosomal machinery in a cap-independent manner (review [38]). Some viruses acquire a cap structure on their mRNA by hijacking the cellular machinery [39] or snatching the cap from cellular mRNA [40,41]. Others synthesize their own cap thanks to virally encoded enzymes [42]. Despite the fact that viruses use different acquisition mechanisms or capping pathways (review [35]), the cap structure of most viruses cannot be distinguished from the cap naturally present on cellular mRNAs.

Viral methyltransferases (MTases) involved in cap methylation belong to the S-adenosyl-L-methionine (SAM) dependent MTase family. 2′-O-MTases can be distinguished by a conserved KDKE catalytic tetrad in close proximity to an RNA binding groove extended by a cap-binding pocket. Thus, upon RNA binding, the 2′-O-MTase transfers the SAM methyl group on the RNA substrate, allowing the 2′-O-methylation of the first nucleotide of the cap structure. Interestingly, 2′-O-MTases are differentially organized among RNA viruses. The L protein of Mononegavirales, such as RSV, and the NS5 protein of Flaviviruses, such as Zika or Dengue virus, is a multifunctional MTase domain carrying both N7- and 2′-O-MTase activities [43–45]. In contrast, Coronaviruses code for two separate enzymes: an N7-MTase at the C-terminal domain of nsp14 and 2′-O-MTase on nsp16, which is positively regulated by nsp10 [46,47]. Similarly, vaccinia virus (VACV) codes for VP39 which corresponds to the 2′-O-MTase [48], while the N7-MTase is encoded in the D1 protein [49].

Internal 2′-O-methylations

Initially, virally encoded MTases were thought to specifically methylate the mRNA cap structures. However, the biochemical characterization of the C-Terminal Domain (CTD) of the Sudan Ebolavirus L protein has recently revealed a cap-independent 2′-O-MTase activity that introduces internal Nm modifications within an RNA template [50*]. Similarly, the NS5 MTase of *Flavivirus*, i.e. West Nile virus (WNV), Dengue virus (DENV) and Zika virus (ZIKV) was also shown to induce internal Nm on adenosines, but with a lower efficiency than what was shown

in vitro for Ebola [44,51]. Remarkably, in the case of DENV and ZIKV, the NS5-induced internal Nm are nucleotide-specific, rather than sequence-specific. Moreover, sensitive mass spectrometry studies have confirmed that DENV and ZIKV genomes carry internal Nm on different nucleotides [3]. Likewise, the genomes of Hepatitis C Virus (HCV), poliovirus (PV) [3], Human Immunodeficiency Virus type 1 (HIV-1) [3,52,53] and murine leukemia virus (MLV) [54] have all been shown to contain Nm modification (all four bases), although none of them encode any known MTase.

This observation raises the question of the involvement of cellular MTases in internal Nm addition to vRNA. The role of a cellular 2′-O-MTase, namely FTSJ3, was elucidated for HIV-1 genome modification. Indeed, FTSJ3 is recruited through the TAR RNA-binding protein (TRBP) and methylates at least 17 specific residues along the gRNA [52]. Nm affect only A (15/17) and U (2/17), with no apparent sequence consensus, but occurs mostly on highly conserved sites among HIV-1 strains. The SARS-CoV-2 genome was also recently shown to contain internal Nm, especially in the 5′ and 3′ UTR regions of the gRNA [17**]. The exact mechanism of internal Nm addition, in this case, remains unknown. However, SARS-CoV-2 interacts with a snoRNA known as SNORD27. This snoRNA is highly suspected to be linked to the viral gRNA 2′-O-methylation, as it interacts with FBL [55], and because several Nm sites are found in the vicinity of the interaction site between SNORD27 and the viral genome.

In terms of quantification, Nm levels measured by mass spectrometry are more abundant on the HIV-1 genome, in comparison to what was found in cells [53]. In the case of the SARS-CoV-2 RNA genome, 130 Nm were detected by Nm-seq [17**], making this RNA 19-fold more affected by these modifications compared to host mRNA analyzed in the same study. Hence, these observations raise legitimate questions about the effects of heavily modified viral genomes on viral replication and mRNA translation into viral proteins.

Roles of 2′-O-methylations during viral replication

Innate immune mechanism of defense against viral infection

Viruses can be detected as foreign microorganisms by intracellular pattern recognition receptor (PRR) related to the innate immune system such as the retinoic acid-inducible gene-I-like receptor (RLRs) and the Toll-like receptor (TLRs). The cytoplasmic RLRs such as RIG-I and MDA5 belong to a helicase family, involved in RNA recognition. RIG-I was initially proposed to specifically detect uncapped, short, and blunt-ended [56] RNA, whereas MDA5 was proposed to coat double-stranded RNA, forming an oligomeric structure (see reviews [57,58**]). After RNA sensing, both RIG-I and MDA5 induce a cascade of intracellular events

leading to the production of type I interferons (IFNs). Subsequently, IFNs bind to interferon-α/β receptors (IFNAR) and promote, by autocrine and paracrine effects, the expression of more than 100 interferon-stimulated genes (ISGs) [59]. Some of these ISGs induce an "antiviral state" or act as restriction factors.

Furthermore, Toll-like receptors (TLRs) are also crucial mediators of the innate immune response, which they can indirectly trigger when they detect pathogen-associated molecular patterns (PAMPs). PAMPS are usually specific motifs exhibited by microorganisms, like viral nucleic acids. The latter are for instance recognized by TLR3 in the case of WNV [60] or PV [61]. Interestingly, Nm limit cytokine and IFN expression induced by TLR7 [62], but the mechanism is currently unknown. However, it might rely on specific sequences or structural features of 2′-O-methylated RNA, thereby acting as an antagonist of TLR7 [62,63]. Hence, Nm are suspected to play a role regarding TLRs sensing.

Proviral roles of 2′-O-methylations

Cap and internal 2′-O-methylations are self markers impairing innate immune sensing

RIG-I is involved in negative-strand RNA virus detection and interacts more specifically with the panhandle of their uncapped viral gRNA [56]. The molecular basis of the interplay of Nm with RNA sensing was elucidated by combining biochemical assay with structural studies on RIG-I. The structure of RIG-I in complex with RNA has revealed that the basic binding cleft of its CTD binds specifically to 5′-triphosphate and cap-0 RNA [64,65]. In addition, the structure shows that the 2′-OH group of the first nucleotide of the RNA interacts directly with Histidine 830 (H830) of RIG-I [66], showing why the 2′-O-methylation of N1 would result in a steric clash with RIG-I [64,65]. This structural observation was confirmed by binding assays showing that the 2′-O-methylation of 5′pppRNA or a cap structure decreases RIG-I affinity by 20 and 200-fold respectively [65]. These studies demonstrate that the 2′-O-methylation of the cap structure is a self-marker that contributes to attenuate RIG-I recognition (**Figure 2**).

During HIV-1 infection, the role of Nm in RLRs-mediated self vs non-self discrimination was further brought to light, as the level of internal Nm appeared to be critical. Hypomethylated HIV-1 genomes produced in FTSJ3-KO cells have been shown to trigger a high production of IFN-α and IFN-β [52]. In this case, it was demonstrated that the early detection of hypomethylated gRNA is mediated by the RIG-like receptor MDA5. Its structure reveals that the presence of Nm within the RNA would result in a steric clash since the protein interacts with RNA 2′-OH groups, thereby limiting the formation of MDA5 concatemers activating the Type-I IFN signaling [67]. Hence, internal Nm camouflage HIV-1 RNA from RLRs sensing

(**Figure 2**).

Moreover, influenza virus and coronaviruses like human coronavirus (HCoV) and mouse hepatitis virus (MHV) are recognized by TLR7 [68,69], a key sensor of ssRNA. It also plays a pivotal role in the inflammatory response triggered by SARS-CoV-2 infection [70]. However, the extent of which Nm modifications found on the SARS-CoV-2 genome [17**] could antagonize the TLR recognition, as is the case for short 2′-O-methylated RNA templates [62,63], remains to be determined.

Eventually, viruses might take advantage of self-markers like Nm to subvert recognition by both RLRs and TLRs.

2′-O-methylated vRNA counteract the antiviral activity of interferon-stimulated genes and restriction factors

2′-O-methylations impede restriction by IFIT proteins

Interferon-induced proteins with tetratricopeptide repeats (IFITs) are involved in the immune antiviral response, as it was demonstrated for WNV infection in mice, where the expression of IFIT-1, IFIT-2 and IFIT-3 increases [71]. Later, the study of WNV infection revealed that the WT virus is lethal, while a mutant devoid of its 2′-O-MTase is not. However, the virulence of the mutant is restored in IFIT-1 KO mice, suggesting that IFIT-1 has a major role in WNV restriction, when the cap of the viral gRNA is not 2′-O-methylated [69] (**Figure 2 & 3**). Other viruses like VACV and MHV, lacking their 2′-O-MTase, are also restricted by IFIT-2 in mouse cells [69]. A more recent study showed that IFIT-1 is the only IFIT protein binding HCoV, thereby allowing the formation of a multiprotein complex with other IFITs [72]. The cooperative action of IFITs would have further antiviral effects. For example, IFIT-1 restricts the translation of miss-capped RNA into active protein by competing with the cap-binding protein EIF4E [72], and IFIT-1 and -2 bind to the translation initiation factor eIF3, as shown upon Sendai virus infection [73]. The molecular basis of the restriction was deciphered following the structural resolution of IFIT-1 in a complex with capped RNA, showing that N1 and N2 methylation of the cap interferes with RNA binding [74].

2′-O-methylations within RNA limit their degradation

Regarding the cap structure, Nm were found to be crucial for preventing the decapping and exonuclease activities of the DXO protein [25,75–77*] (**Figure 3**). How the cap 2′-O-methylation might counteract DXO during viral replication remains to be demonstrated. Nevertheless, as this enzyme seems to target the HCV genome when it is not protected by a

miRNA at its 5′ end [78], it might be relevant to look for the role of DXO as a restriction factor during viral infection.

The protective role of Nm against 3′ end RNA degradation by exonucleases was also demonstrated in *Caenorhabditis* and *Arabidopsis.* Indeed, in these experimental models, Nm were evidenced to protect Piwi-interacting RNA (piRNA) [26*] or microRNA [79] respectively, from 3′ exonuclease degradation. We suspect it to be a common mechanism within RNA viruses, since we recently demonstrated that Nm confer protection against ISG20, which is an interferon-induced exonuclease with an antiviral activity [80,81], acting as a restriction factor on hypomethylated viruses [27]. Using biochemical experiments, it was demonstrated that ISG20 mediates the 3′ end degradation of RNA lacking Nm, whereas the addition of Nm almost completely blocked the exonuclease degradation of RNA (**Figure 2 & 3**). The structure-function analysis revealed that the nuclease activity was inhibited through a steric clash between the Nm and ISG20 residues Arginine 53 and Aspartic acid 90 located in the putative RNA-binding site. Moreover, we confirmed that retrotranscription of hypomethylated HIV-1 genomes, produced in FTSJ3-KO cells, was impaired in T cells by interferon-induced ISG20, demonstrating the direct antagonist effect of Nm on ISG20-mediated antiviral activity in infected cells [27].

The cellular epitranscriptomic machinery is regulated by viral infection

In the case of HIV-1 infection, the cellular FTSJ3 enzyme is recruited by TRBP in the nucleus [52]. However, FBL, another nuclear 2′-O-MTase, is relocated to the cytoplasm during Hendra and Nipah intra-cytoplasmic infection [82] and might be recruited by SNORD27 during cytoplasmic replication cycle of SARS-CoV-2 [17**]. Thus, as cellular enzymes are redirected or sequestrated by viruses, we could enquire about the consequences on the level of Nm in cells. Indeed, Yang et al., (2021) have demonstrated that upon infection, the 2′-O-methylation profile of the SARS-CoV-2 genome increases while that of the host RNA significantly declines [17**]. The deregulation of the level of methylation happens similarly with N6-methylation during HBV [83], and HIV-1 [84] infections, suggesting that viruses widely interfere with cellular processes, such as RNA modification addition. It can then negatively impact the pool of cellular RNA.

Antiviral roles of 2′-O-methylations

2′-O-methylations impair viral genome replication

Interestingly, Nm are not only linked to proviral effects as they can interfere with key steps of the viral life cycle. For example, gRNA 2′-O-methylation has been reported to limit the activity of the DENV polymerase [51]. Moreover, the reverse transcriptase (RT) of MLV pauses before an Nm site on an RNA template at low dNTP concentrations, impairing reverse transcription *in vitro* [85] (**Figure 3**). Consequently, the role of cellular or even viral 2′-O-MTases might be ambivalent, as they seemingly ensure the success of viral replication, which comes at a cost to genome replication/transcription. Furthermore, the expression of several cellular 2′-O-MTases is prone to be stimulated by IFN, as annotated in the Interferome v2.0 database [86] (**Table 1**) and in [87], raising the question as to the potential role of cellular MTases as restriction factors.

2′-O-methylations could disrupt vRNA translation

It was first proposed that Nm found on the DENV genome slightly reduces translation [51]. To go further, we could extrapolate some findings related to eukaryotic cells. As Nm disrupt tRNA pairing when found in the middle of a codon [16,22], such a modification could impair vRNA translation. This remains to be confirmed for modified viral gRNA. However, regarding the SARS-CoV-2 2′-O-methylated genome, position 2 of codons within the viral genome is devoid of Nm [17**], possibly because viruses carrying vRNA modified at this position are counter-selected. For the moment, the effect of Nm on interactions with the translation machinery can only be inferred (**Figure 3**), and the impact of vRNA Nm on structure, splicing, co-transcriptional protein-binding interactions, ribosome recruitment, trafficking, nuclear export and encapsidation remains unknown.

Conclusion

As a conclusion, this review emphasizes the role of Nm in the world of RNA viruses. No less than 188 zoonotic viruses infect humans, 159 of which are RNA viruses [88]. Consequently, it is of major importance to carry out a refined analysis of the presence and derived effects of epitranscriptomic marks on viral genomes, in order to further understand their role in the replication.

Several recent works have addressed the pro- and anti-viral role of Nm. It seems that most viruses decorate their genome with Nm to disguise their RNAs, thereby avoiding detection and degradation by innate immune sensors and effectors. Interestingly, the innate

eukaryotic mechanism of foreign RNA recognition is reminiscent of how bacterial restriction enzymes target the phage DNA. In this case, evolution has also selected the methylation process to protect DNA against restriction enzymes.

Finally, the most comprehensive picture of how Nm affect the viral replication cycle is depicted for HIV-1, as Nm allow to escape the innate immune detection by MDA5 after the viral entry [52], then protect the vRNA against degradation mediated by ISG20 at early stages [27], and are added by the actively recruited cellular FTSJ3 after the transcription of the viral genome at later stages [52]. To unravel how epitranscriptomic modifications regulate the replication cycle of other viruses, it is necessary to further elucidate the spatial and temporal regulation of Nm modification machinery upon viral infection. We need to map precisely the different positions targeted by Nm in viral gRNA, mRNA or other vRNA species and to determine when the Nm addition occurs during the viral life cycle. We also need to identify the viral or cellular enzymes involved in Nm addition, in order to understand how these modifications hijack or counter cellular mechanisms. This can now be achieved thanks to new Nm mapping techniques, combined with the growing interest in deciphering the role of these vRNA epitranscriptomic modifications.

Perspectives

Since limiting the activity of 2′-O-MTases would restore the early detection of viruses and drive an efficient antiviral response, these enzymes can be considered as potential therapeutic targets. However, this approach should be treated with caution regarding the complexity of these processes. On one hand, specific inhibition of viral MTases involved in capping or internal Nm addition could be expected to result in a strong impairment of vRNA translation and increased detection by sensors like RIG-I, or MDA5 respectively. On the other hand, off-target effects on cellular 2′-O-MTases might be toxic for the cells. Conversely, potentiating the activity of some specific cellular 2′-O-MTases, by mRNA or IFNs treatments, might drastically increase the level of internal Nm within some vRNA, thereby limiting viral genome replication.

Interestingly, mutated viruses lacking 2′-O-methyltransferase activity were shown to be good candidates for the rational design of attenuated vaccines, since they are more sensitive to the detection or action of immune sensors and effectors [89]. Ultimately, knowledge about the regulation of Nm would help with the use of mRNA for both vaccines and anti-cancerous treatments for instance. Indeed, inducing Nm at specific sites (cap N1 or N2, or internal positions) might help to better control the elicitation of innate immunity, protein translation or RNA stability.

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Declarations of interest

None.

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Figures

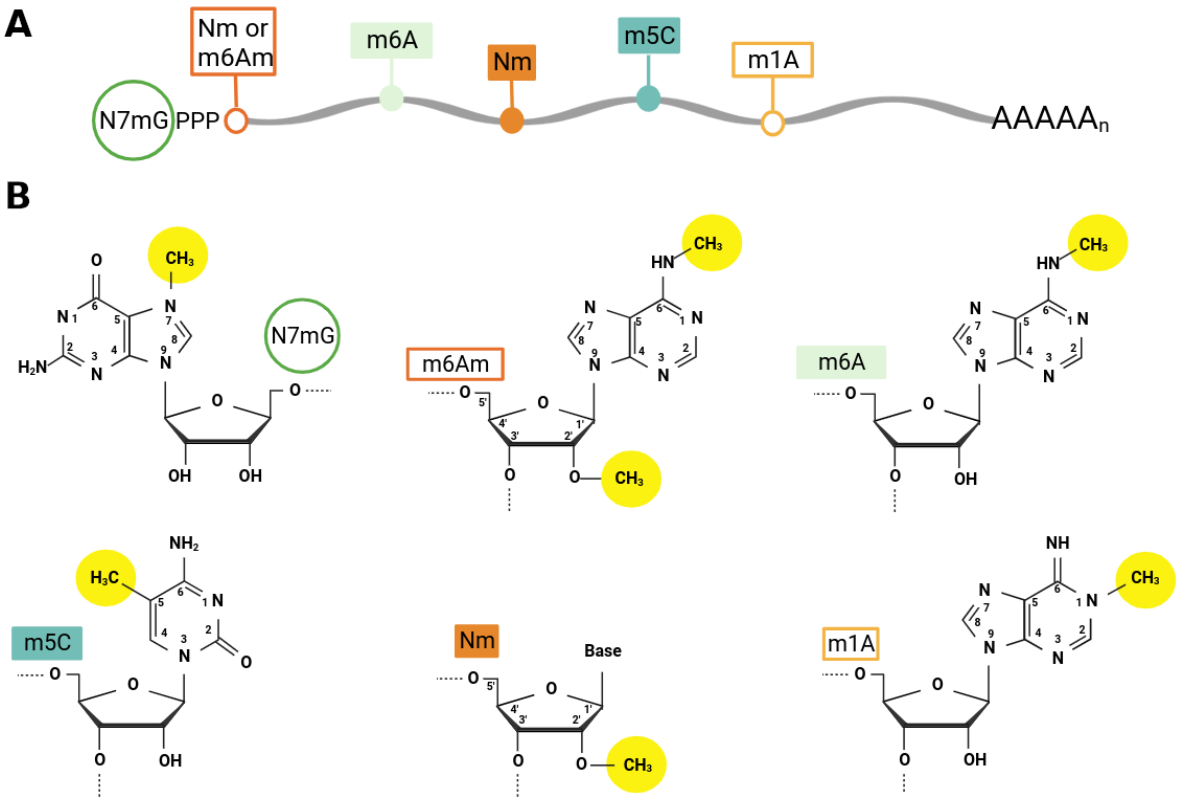


Figure 1. Principle known methylations affecting RNA. A) Example of an mRNA modified by a 5′-cap structure, internal 2′-O-methylations, and a 3′-polyA tail. N7mG, N7-Methylguanosine; m6Am, N6,2′-O-dimethyladenosine; m6A, N6-Methyladenosine; m5C, N5-Methylcytosine; Nm, 2′-O-methylation; m1A, N1-Methyladenosine. B) Representation of

modified nucleobases and riboses from the mRNA presented in panel A. Methyl groups are highlighted in yellow.

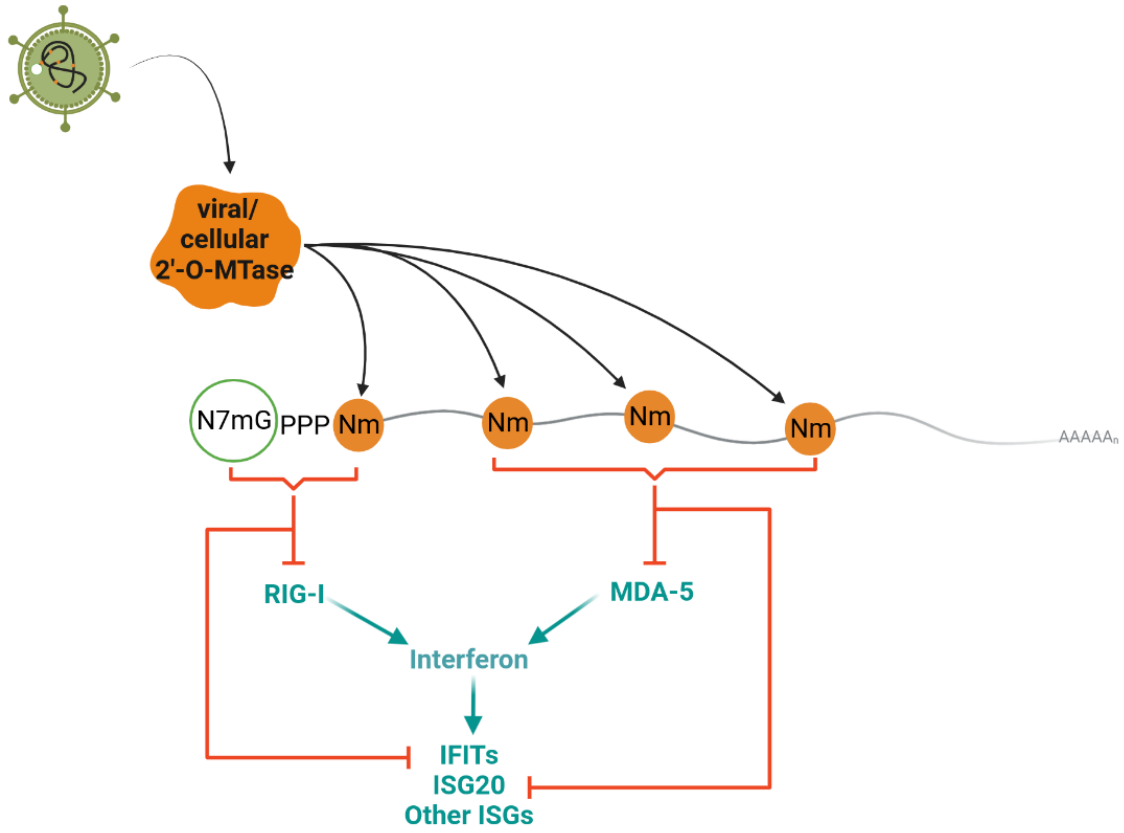


Figure 2. 2′-O-methylations on viral RNA mimic self-markers. The presence of cap and internal 2′-O-methylations inhibit innate immune sensing and the antiviral response mediated by IFN induced restriction factors. Cap 2′-O-methylation prevents RIG-I detection, while internal 2′-O-methylations inhibit MDA5 detection. Conversely, miss-capped or hypomethylated RNA are detected by RIG-I and MDA5 respectively, and trigger intracellular signaling cascades leading to the production of Type I Interferon-Stimulated Genes (ISGs). ISGs like IFITs target mis-capped RNA and block the viral mRNA translation into proteins, while ISG20 exonuclease degrades hypomethylated mRNA. However, the presence of vRNA 2′-O-methylations at the 5′ or 3′ end of RNA impairs the recruitment of IFITs and the degradation mediated by other ISGs.

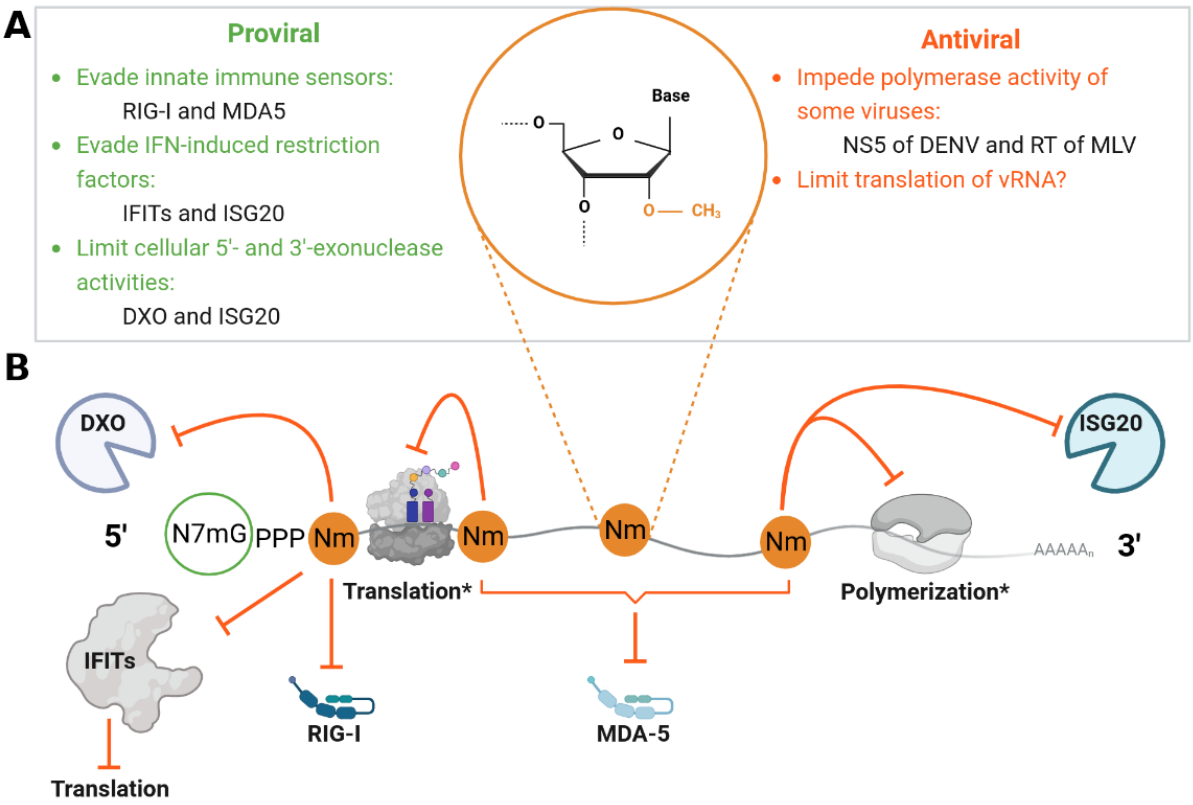


Figure 3. Proviral and antiviral roles of 2′-O-methylations. A) List of pro- and antiviral roles of 2′-O-methylations currently documented or suspected. DENV, Dengue virus; MLV, Murine Leukemia virus. B) Interactions between RNA molecules and cellular actors affected by 2′-O-methylations. Antiviral roles of 2′-O-methylations are marked with an asterisk.

Table

Table 1. Examples of human 2′-O-methyltransferases annotated as interferon-regulated genes in the database Interferome v2.0 [86].

Gene Name	Description	Gene ID	Type of IFN
CMTR1	cap methyltransferase 1	23070	I, II
TARBP1	TAR (HIV-1) RNA binding protein 1	6894	I
TRMT13	tRNA methyltransferase 13 homolog	54482	II

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