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Clinical Immunology 226 (2021) 108699

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

The role of A-to-I RNA editing in infections by RNA viruses: Possible implications for SARS-CoV-2 infection

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ARTICLE INFO

Keywords:
SARS-CoV-2
Mutations
A-to-I RNA editing
Viral infections
Innate immunity

ABSTRACT

RNA editing is a fundamental biological process with 2 major forms, namely adenosine-to-inosine (A-to-I, recognized as A-to-G) and cytosine-to-uracil (C-to-U) deamination, mediated by ADAR and APOBEC enzyme families, respectively. A-to-I RNA editing has been shown to directly affect the genome/transcriptome of RNA viruses with significant repercussions for viral protein synthesis, proliferation and infectivity, while it also affects recognition of double-stranded RNAs by cytosolic receptors controlling the host innate immune response. Recent evidence suggests that RNA editing may be present in SARS-CoV-2 genome/transcriptome. The majority of mapped mutations in SARS-CoV-2 genome are A-to-G/U-to-C(opposite strand) and C-to-U/G-to-A(opposite strand) substitutions comprising potential ADAR-/APOBEC-mediated deamination events. A single nucleotide substitution can have dramatic effects on SARS-CoV-2 infectivity as shown by the D614G(A-to-G) substitution in the spike protein. Future studies utilizing serial sampling from patients with COVID-19 are warranted to delineate whether RNA editing affects viral replication and/or the host immune response to SARS-CoV-2.

1. Introduction

Currently, more than 170 known RNA base modifications expand the RNA alphabet from 4 to hundreds of individual nucleotides [1]. The most abundant RNA modification in humans is RNA editing, which comes in 2 main forms, namely adenosine-to-inosine (A-to-I) and cytosine-to-uracil (C-to-U) deamination, mediated by the ADAR and APOBEC family of enzymes, respectively [2–4]. Inosine (I) is in turn recognized as guanosine (G) by polymerases during RNA-dependent RNA replication (viral replication) and by ribosomes during translation [2,5,6]. A-to-I RNA editing is a widespread phenomenon in the human transcriptome, mainly located in the endogenous *Alu* retroelements, which locally form double-stranded RNA regions, a pre-requisite for the binding and catalytic deamination by ADARs [7,8]. A-to-I RNA editing has been shown to affect multiple facets of the RNA metabolism [2,5,9], while we and others have previously shown that ADAR1-induced RNA editing is enhanced under chronic inflammatory conditions leading to stabilization of proinflammatory transcripts, thus having a "fuel-on-fire" effect on the perpetuation of the inflammatory response [10,11]. More importantly, A-to-I RNA editing has been shown to directly affect the genome and transcriptome of RNA viruses with significant repercussions for viral protein synthesis, proliferation and infectivity [6,12]. Of interest, recent data suggest that RNA editing may also take place in the genome/transcriptome of SARS-CoV-2, the virus responsible for the ongoing COVID-19 pandemic.

2. Single nucleotide variants in SARS-CoV-2 genome: hints towards the involvement of host RNA editing machineries

As of February 2021, COVID-19 accounts for more than 2 million deaths worldwide. Despite the intensive efforts of the scientific and medical community, there is currently no available targeted therapy, while numerous vaccines are in the stage of clinical trials with only a few having reached the clinic. SARS-CoV-2 has an approximately 30

Abbreviations: eIF-2a, Eukaryotic translation initiation factor 2 subunit 1; *IFN*, interferon; *IRF*, interferon regulatory factor; *ISG*, interferon stimulated genes; *MDA-5*, melanoma differentiation-associated protein 5; *PKR*, protein kinase R; *RIG-I*, retinoic acid-inducible gene I..

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https://doi.org/10.1016/j.clim.2021.108699
Received 23 November 2020; Received in revised form 21 February 2021; Accepted 22 February 2021
Available online 25 February 2021
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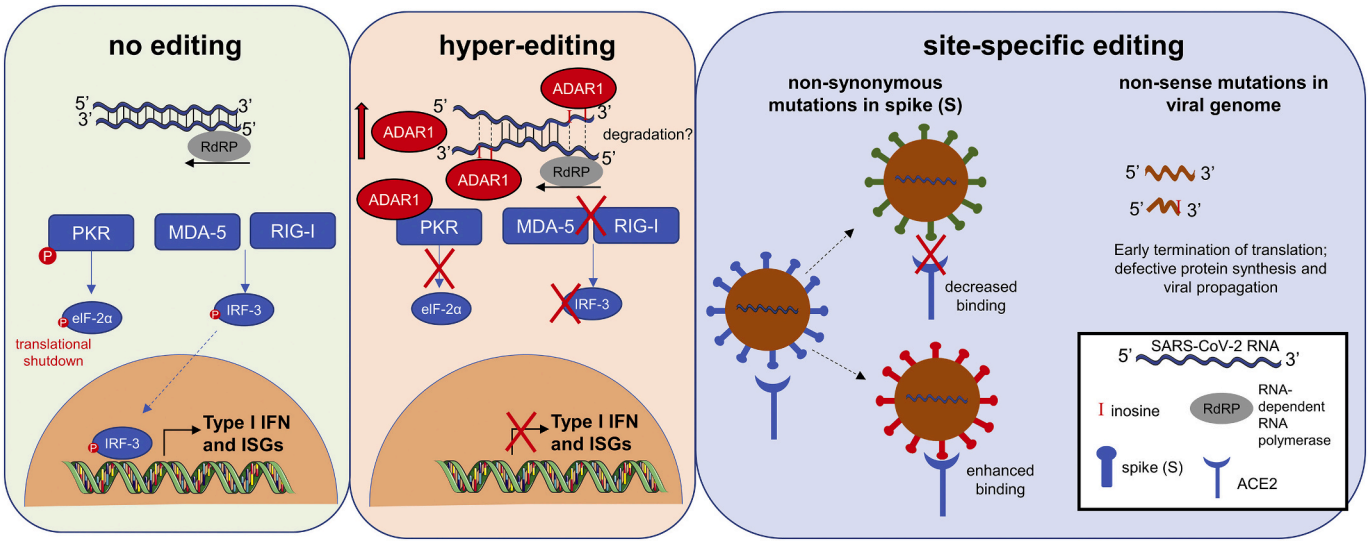

Fig. 1. A-to-I RNA editing of SARS-CoV-2: potential consequences on the host-virus interactions. **Left panel.** Double-stranded RNA of SARS-CoV-2 formed during replication can be recognized by cytosolic innate immune receptors MDA-5 and RIG-I leading to the activation of type I interferon (IFN) pathway, as well as hyper-activation of PKR, which ultimately leads to translational shutdown. **Middle panel**. Extensive A-to-I editing of the double-stranded RNA structure by ADAR enzymes could potentially prevent its recognition by innate immune receptors. Moreover, increased ADAR1 can directly interact with PKR preventing its hyper-activation. On the other hand, extensively edited dsRNA can be selectively degraded by endonucleases underlining the complex balance between pro- and anti-viral editing effects. **Right panel.** Site-specific RNA editing can have either pro-viral or anti-viral effects. A-to-I (G) substitutions in the SARS-CoV-2 spike protein can alter binding to ACE2 through various mechanisms including binding affinity, spike conformation or loading of the spike into virions, subsequently affecting viral infectivity. One such example is the D614G substitution (A-to-G point mutation; unknown origin) which has increased viral infectivity by ~10-fold. On the other hand, a non-sense mutation in one of the viral transcripts could prohibit viral protein synthesis and propagation. Certain items on this figure have been adapted from Servier Medical Art by Servier (https://smart.servier.com – licensed under Creative Commons Attribution 3.0 Unported License).

kilobases long, positive-sense, single-stranded RNA genome [13,14]. International efforts have provided early accurate sequencing of the viral genome [14], while the use of nanopore direct RNA sequencing has enabled the detection of base modifications creating a detailed transcriptomic and epitranscriptomic map of SARS-CoV-2 at single base resolution [15]. Detection of single nucleotide variants (SNVs) in the viral genome has gained significant attention with recent studies showing that substitutional mutations in the spike protein of SARS-CoV-2 may greatly affect its virulence and transmissibility [16,17].

In a recent paper examining 33,693 complete SARS-CoV-2 genome sequences, C-to-U (~24%) was the most common base substitution, while A-to-G (~15%) and U-to-C (~14.5%) followed [18]. Base substitutions can be divided into two main categories: transitions [purine-to-purine (A↔G) and pyrimidine-to-pyrimidine (U↔C)] and transversions (change between a purine and a pyrimidine) [19]. Transitions take place more easily, since they do not require the addition or removal of ribose rings, and bear a lower risk to lead to detrimental amino-acid changes [19]. Therefore, they are generally more common in both viral and human genome throughout evolution [19]. However, the surprisingly high percentage of transitions (~65%) in SARS-CoV-2 genome raises another interesting possibility: the involvement of host RNA editing machinery. In line with this, a recent report showed that 87% of the synonymous substitutions observed between SARS-CoV-2 and the bat coronavirus RaTG13 could be potentially attributed to deamination of cytosines (65%) and adenosines (22%), respectively, through the host RNA editing machinery [20].

APOBECs are enzymes that mediate the deamination of cytosine-to-uracil (C-to-U), which, depending on the sequencing strand, can also be viewed as G-to-A. Similarly, the deamination of adenosine-to-inosine (A-to-I) by ADARs, which leads to an adenosine-to-guanosine (A-to-G) substitution, can also be detected as U-to-C when in the opposite strand. While we cannot exclude the possibility that the increased presence of C-to-U and A-to-G mutations in SARS-CoV-2 may have occurred through random mutation events, a series of factors suggest the involvement of host RNA editing machinery:

1) The observed frequency of SNVs does not follow the pattern of RNA-dependent RNA polymerase (RdRP) errors, as revealed by previous mechanistic studies removing the 3➔5′ exoribonuclease activity ("proofreading") of coronavirus [21].
2) C-to-U substitutions observed in SARS-CoV-2 genome/transcriptome follow the APOBEC deamination motif [A/U]C[A/U] [3,22–24]. C residues surrounded by A/U both upstream (5′) and downstream (3′) were ~ 10-fold more likely to be substituted by U compared to C residues surrounded by either G or C [24].
3) A-to-G substitutions in SARS-CoV-2 genome show a depletion of G at −1 position [22,25], and a slight G enrichment 1-base downstream [25], which is also observed in human ADAR1/2-induced A-to-I editing events [26].
4) the increased frequency of A-to-G base substitutions in association with increased type I interferon (IFN) response and ADAR1 expression in Calu-3 cells infected with SARS-CoV-2 supports the potential involvement of the interferon-inducible ADAR1p150 enzyme [25].

In a first report utilizing nanopore direct RNA sequencing, researchers detected at least 41 RNA modification sites on viral transcripts [15]. Of interest, modified viral RNAs had shorter poly(A) tails than unmodified RNAs, suggesting that RNA modifications may affect RNA stability and consequently viral protein synthesis [15]. While this initial report excluded the presence of A-to-I RNA editing events, later studies have detected multiple RNA editing sites in the SARS-CoV-2 transcriptome and genome [22,25]. Di Giorgio et al. used bronchoalveolar lavage fluid (BALF) samples from patients with COVID-19 to examine the presence of RNA editing events in SARS-CoV-2 transcriptome [22]. Using metagenomic sequencing they analysed 8 samples of appropriate sequencing depth and detected multiple base substitutions in SARS-CoV-2 transcriptome with A-to-G being the most prevalent. Of note, depletion of G bases in position −1 of the A/G substitutions was evident in SARS-CoV-2 samples supporting the involvement of ADARs [22]. Similarly, C-to-U substitutions following a motif compatible with APOBEC editing were detected in the examined SARS-CoV-2 transcriptome. Of note, 9

Table 1
The role of ADAR1 and ADAR2 in viral RNA infections*

Virus	Main "editor"	Model of study	Editing sites	Treatment - ADAR overexpression/ knockdown	Key findings	Ref.
HCV	ADAR1 p150	*In vitro* Huh-7 cells	Radiolabeled AMP	IFNα treatment	Increased A-to-I editing of radiolabeled AMP. Inhibition of HCV replicon (BB7) synthesis.	[46]
				ADAR1-knockdown	5- to 41-fold increase of HCV replicons.	
				ADAR2-knockdown	No effect on HCV replicons.	
HDV	ADAR1	*In vitro* Huh-7, HEK293 cells	HDAg (A1012) ("Amber/W" site)		HDAg-L production Switch from replication to packaging	[28–30]
	ADAR1	*In vitro* Huh-7, HEK293 cells	HDAg (A1012) ("Amber/W" site)	ADAR1-knockdown	Inhibition of HDV-antigenome editing. Reduced production of HDV virions. ADAR1p110 is primarily responsible for HDV antigenome editing during replication.	[47,48]
	ADAR1/ ADAR2	*In vitro* Huh-7 cells	HDAg (A1012) ("Amber/W" site)	IFNα treatment (ADAR1p150 up-regulation) ADAR1/ ADAR2 overexpression	Increased editing of amber/W site. Hyper-editing at non-amber/W sites inhibited HDV RNA replication. Increased HDAg-L production. Inhibition of HDV replication. ADAR1p150 is mainly responsible for IFNα-induced HDV RNA editing.	[49–51]
HIV-1	ADAR1	*In vitro* COS-7, HEK293T cells	env	ADAR1 overexpression	Upregulation of p24 Gag protein expression	[52]
				Catalytically-inactive ADAR1 overexpression	No effect on p24 Gag protein expression	
				ADAR1-knockdown	Downregulation of p24 Gag protein expression.	
	ADAR1	*In vitro* HEK293T, Jurkat-T cells *Ex vivo* Primary $CD4^+$ T cells	5' UTR, rev, tat	ADAR1-overexpression	Significantly increased release of HIV virions. Increased viral infectivity in primary human $CD4^+$ T cells.	[53]
				Catalytically-inactive ADAR1 overexpression	No significant effect on HIV virions' release or viral infectivity.	
	ADAR2	*In vitro* HEK293T, Jurkat T cells	5' UTR	ADAR2-overexpression	Significantly increased release of HIV virions. No effect on viral infectivity.	[54]
				Catalytically-inactive ADAR2 overexpression	No effect on HIV virion release or viral infectivity.	
				ADAR2-knockdown	Impaired HIV protein synthesis and replication.	
	ADAR1	*Ex vivo* PBMCs, primary $CD4^+$ T cells	n/a		Decreased HIV replication in Aicardi Goutières Syndrome (defective ADAR1) compared to healthy control-derived PBMCs.	[55]
		In vitro Jurkat T cells		ADAR1-knockdown	Inhibition of viral protein synthesis and replication.	
	ADAR1 p150	*In vitro* HEK293T, Jurkat T, HeLa cells *Ex vivo* Primary $CD4^+$ T cells	rev, env	IFNα treatment (ADAR1p150 up-regulation)/ADAR1-overexpression	Inhibition of HIV protein synthesis and viral infectivity.	[56]
				Catalytically-inactive ADAR1 overexpression	No significant effect on viral protein synthesis or infectivity.	
	ADAR1 p150	*Ex vivo* Macrophages, BALF cells	Envelope gp120 V3	IFN-γ treatment (ADAR1p150 up-regulation)	Increased A-to-I editing of the viral envelope RNA in BALF cells of aerosol IFN-γ-treated patients. Inhibition of HIV replication.	[40]
				ADAR1-knockdown	Increased viral infectivity.	
				ADAR2-knockdown	No effect on viral infectivity.	
Influenza A	ADAR1	*In vitro* HEK293T, A549 cells	Reporter plasmid		NS1-ADAR1 interaction increases ADAR1-mediated editing and viral protein expression.	[31]
				Catalytically-inactive ADAR1 overexpression	Decreased viral protein expression.	
				ADAR1-knockdown	Decreased viral protein expression and viral production.	
Measles Virus	ADAR1 p150	*In vitro* Vero, HeLa cells	Defective Interfering (DI) RNAs		Several measles virus DIs had a large number of A-to-G substitutions, suggestive of ADAR1-mediated A-to-I editing.	[57]
SARS-CoV-2	ADAR1	BALF samples	viral transcriptome/ genome		Several A-to-G/ U-to-C mutations were observed in SARS-CoV-2 transcriptome (most common single nucleotide variants). Significantly fewer A-to-G/U-to-C substitutions were detected in the viral genome. No nonsense A-to-G/U-to-C substitutions were detected in SARS-CoV-2 genome or transcriptome, proposing a potential deleterious effect for SARS-CoV-2 replication.	[22]
		Calu-3, Vero cells	viral genome/ transcriptome		Multiple A-to-G/U-to-C substitutions were detected in viral genome (>300 unique A-to-G sites identified). Increased A-to-G substitutions 12 h-24 h post-infection of Calu-3 cells with SARS-CoV-2 *in vitro* coincided with increase of type I interferons and ADAR1. 96% of the observed substitutions in hyper-edited transcripts occurred in exonic sequences and frequently (64%) led to amino-acid substitutions	[25]

Abbreviations: *HCV*: hepatitis C virus; *HDV*: hepatitis D virus; *HIV*: human immunodeficiency virus; *BALF*: bronchoalveolar lavage fluid,

* The Table includes the main results from selected publications on the role of ADAR1/2 in RNA viral infections and does not comprise an exhaustive literature review.

(~8.5%) of the observed C-to-U/G-to-A substitutions, but no A-to-G/U-to-C substitutions, led to the creation of a stop codon (nonsense mutations) in the transcriptomic data. Interestingly, none of these 9 nonsense mutations were present in genomic data of SARS-CoV-2 raising the possibility that such editing events may be incompatible with SARS-CoV-2 propagation (Fig. 1) [22].

In a later study, Picardi et al. validated the presence of A-to-G substitutions in SARS-CoV-2 genome consistent with the ADAR1/2-induced RNA editing motif [25]. Moreover, the researchers detected hyper-edited reads [27] (reads with excessive editing that do not easily align to the genome) where A-to-I events accounted for more than 75% of the detected substitutions [25]. Of note, 96% of the observed substitutions in hyper-edited reads occurred in exonic sequences and frequently (64%) led to amino-acid substitutions [25]. More importantly, the authors showed that A-to-G base substitutions were enriched after infection of lung epithelial cells (Calu-3) with SARS-CoV-2 *in vitro*, coinciding with the spiked increase of type I IFN and ADAR1 expression [25]. Finally, A-to-G and U-to-C substitutions were observed with equal frequency in both studies [22,25], further supporting the involvement of ADARs which act on double-stranded RNA substrates.

3. The role of A-to-I RNA editing in infections by RNA viruses: possible implications for SARS-CoV-2 infection.

A-to-I RNA editing has been previously recognized as a determining factor for the fate of multiple RNA viruses including HIV-1, HCV, HDV, Influenza A and Measles virus (Table 1). Host-dependent A-to-I RNA editing of the viral genome or transcriptome can have either pro-viral or anti-viral effects depending on the host-virus interaction (excellently reviewed in [6]). A-to-I RNA editing in coding regions may affect protein synthesis and consequently proliferation and infectivity of the virus (Table 1 and Fig. 1). An excellent example of this comes from the hepatitis delta virus (HDV): HDV encodes two forms of the Hepatitis Delta Antigen (HDAg) protein, namely a shorter form (p24 / HDAg-S) that is essential for viral RNA replication, and a longer form extended by 19 amino acids (p27 / HDAg-L), which facilitates packaging of the viral genome and viral particle assembly [6]. A-to-I editing of a stop codon (UAG, "amber") is necessary to turn it into tryptophan [UI(=G)G, "W"] thus enabling the production of HDAg-L [28–30] (Table 1). Moreover, ADAR1 may interact with viral proteins, such as Influenza A NS1, through its RNA-binding domains with potential implications for type I IFN pathway activation [31]. Viruses may take advantage of the host RNA editing machinery to avoid recognition by innate immune receptors. More specifically, previous studies have shown that dsRNAs containing multiple IU-pairs suppress the activation of the innate immune receptors MDA5 and RIG-I and subsequently IRF-3, thus inhibiting the induction of the type I IFN pathway [32] (Fig. 1). Similarly, ADAR1 can directly interact with the antiviral PKR protein and prevent its hyperactivation thus promoting viral replication [33–36].

Type I IFN seems to be the determining factor of host response to SARS-CoV-2 [37]. ADAR1, and specifically the cytoplasmic ADAR1p150 isoform, is IFN-inducible [38], suggesting a potential involvement of ADAR1-induced RNA editing in the host immune response to SARS-CoV-2. However, SARS-CoV-2 seems to avoid extensive A-to-I RNA editing as shown by the low levels (<1%) of A-to-I editing detected in the isolated viral genomes/transcriptomes from patient cells [22,25], which is in line with low type I IFN-induced gene expression observed in SARS-CoV-2 infected cells [39]. Whether exogenous IFN administration to COVID-19 patients could affect viral replication partly through induction of multiple RNA editing events (hyper-editing) that can inhibit viral protein synthesis, as has been previously shown for HIV-1 [40], or mark dsRNA for degradation by specific endonucleases [41], remains to be proven by future studies.

Finally, the best-studied SARS-CoV-2 mutation to date leading to an amino-acid substitution (D614G) in the spike protein affecting viral binding to ACE2 and consequently cellular entry and virulence is indeed an A-to-G substitution [16]. Whether this was originally an ADAR1-mediated RNA editing event cannot be proven, however it supports the significant repercussions of single nucleotide substitutions in the spike protein for SARS-CoV-2 infectivity [16,17] through various mechanisms including ACE2 binding affinity [42], conformational changes leading to an ACE2 binding-competent state [43] or higher availability of spike protein in virions [44]. With CRISPR-Cas13 being intensively investigated in the last few years [45], identification of deleterious A-to-G substitutions in the SARS-CoV-2 genome through computational modeling and validation of reduced proliferation/infectivity *in vitro* could unravel new, targeted therapeutic approaches. Finally, future studies examining sequential samples from patients with different disease course could shed more light on the up- or down-regulation of RNA editing in patients and its association with viral replication and host innate immune response during the early stages of disease (type I IFN-mediated immunity) or during the hyper-inflammatory syndrome observed later on.

In conclusion, the widespread nature of RNA editing and its established role in viral infections, the inducible character of ADAR1 by interferon and other proinflammatory cytokines, and the potential of single base substitutions to significantly alter the infectivity of SARS-CoV-2 along with the establishment of CRISPR-Cas13, make RNA editing worth exploring in the COVID-19 pandemic.

Author contributions

NIV and KMV performed literature search. NIV wrote the 1st draft of the manuscript after input from all authors. All authors reviewed the manuscript and approved the final version.

Declaration of Competing Interest

none.

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