Zhu *et al. Biology Direct* (2023) 18:12
https://doi.org/10.1186/s13062-023-00366-w

Biology Direct

REVIEW

Open Access

Host-mediated RNA editing in viruses

Tongtong Zhu[1,2,3], Guangyi Niu[1,2,3], Yuansheng Zhang[1,2,3], Ming Chen[1,2,3], Chuan-Yun Li[4], Lili Hao[1,2*] and Zhang Zhang[1,2,3*]

Abstract

Viruses rely on hosts for life and reproduction, cause a variety of symptoms from common cold to AIDS to COVID-19 and provoke public health threats claiming millions of lives around the globe. RNA editing, as a crucial co-/post-transcriptional modification inducing nucleotide alterations on both endogenous and exogenous RNA sequences, exerts significant influences on virus replication, protein synthesis, infectivity and toxicity. Hitherto, a number of host-mediated RNA editing sites have been identified in diverse viruses, yet lacking a full picture of RNA editing-associated mechanisms and effects in different classes of viruses. Here we synthesize the current knowledge of host-mediated RNA editing in a variety of viruses by considering two enzyme families, viz., ADARs and APOBECs, thereby presenting a landscape of diverse editing mechanisms and effects between viruses and hosts. In the ongoing pandemic, our study promises to provide potentially valuable insights for better understanding host-mediated RNA editing on ever-reported and newly-emerging viruses.

Keywords Virus, RNA editing, Deamination, Proviral, Antiviral

Introduction

RNA editing, as a crucial co-/post-transcriptional modification inducing nucleotide alterations on both endogenous and exogenous RNA sequences [1–3], plays important roles in many biological processes in nearly all forms of cellular life [4–7] and is associated with a variety of human diseases, including cancers [8, 9]. In metazoans, primary RNA editing types are adenosine to inosine (A-to-I; inosine is further recognized as guanosine) and cytidine to uridine (C-to-U), which are catalyzed by adenosine deaminases acting on RNA family (ADARs, including ADAR1, ADAR2, and ADAR3) and apolipoprotein B mRNA editing catalytic polypeptide-like family (APOBECs, including APOBEC1, APOBEC2, APOBEC3A-H, APOBEC4, and AID), respectively [4, 8, 10–15]. In addition to deamination activity, ADARs and APOBECs, also acting as RNA binding proteins, could interact with RNA targets directly and thus exert extra complicated molecular effects on biological functions of both endogenous and exogenous RNAs, especially virus RNAs [16–18].

Viruses rely on hosts for life and reproduction, cause a variety of symptoms from common cold to AIDS to COVID-19 and provoke public health threats claiming millions of lives around the globe. Over the past decades, a number of studies have experimentally revealed complicated mechanisms between various viruses and their hosts mediated by RNA editing (Fig. 1). A case in point is the first discovery reported in 1992 that host-mediated RNA editing regulates the packaging and inhibits the

*Correspondence:
Lili Hao
haolili@big.ac.cn
Zhang Zhang
zhangzhang@big.ac.cn
[1]National Genomics Data Center & CAS Key Laboratory of Genome Sciences and Information, Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100101, China
[2]China National Center for Bioinformation, Beijing 100101, China
[3]University of Chinese Academy of Sciences, Beijing 100049, China
[4]Laboratory of Bioinformatics and Genomic Medicine, Beijing Key Laboratory of Cardiometabolic Molecular Medicine, Institute of Molecular Medicine, Peking University, Beijing 100871, China

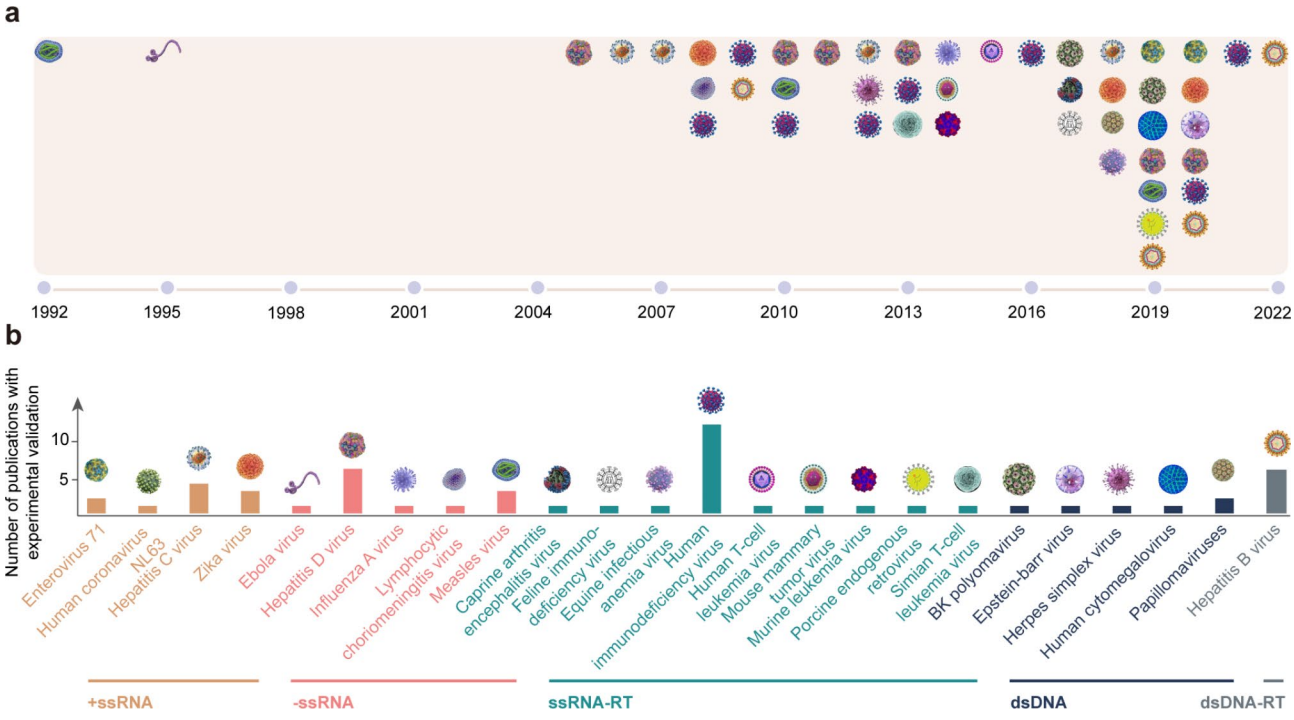

Fig. 1 RNA editing events in viruses. **(a)** The timeline of host-mediated RNA editing events identified in viruses with experimental validation. **(b)** Number of experimentally validated publications in different classes of viruses

replication of hepatitis D virus [19]. Based on the deaminase roles during the process of virus infection, the interaction between RNA editing enzymes and viruses can be classified into two categories, namely, deamination-dependent (cis-regulation) and deamination-independent (trans-regulation) [20]. For the former, ADARs and APOBECs catalyze the hydrolytic deamination directly on viral RNA substrates [21], which can provoke viral RNA sequence variations [22], changes of viral RNA secondary structures [73], and amino acid recoding [23]. For the latter, ADARs and APOBECs can be involved in host immune response pathways without deamination but interact with viral proteins, viral RNAs, or other host immune factors [24–26]. Regardless of whether deamination is dependent or independent, host-mediated RNA editing can substantially influence the viral life cycle, host adaptation, or evolutionary directions to some extent [21, 27, 28]. Moreover, host-mediated RNA editing can lead to either proviral or antiviral effect on viruses [29], corresponding to increased viral fitness or diminished viral growth, respectively. Specifically, the proviral effect helps viruses evade the host immune response through promoting virus replication [30] and protein synthesis [31] as well as reducing virus toxicity [32]. Contrastingly, the antiviral effect works against a broad range of viruses through inhibition of virus replication [33] or reverse transcription [34].

To date, a wealth of RNA editing sites have been detected in different classes of viruses except single-stranded DNA (ssDNA) and double-stranded RNA (dsRNA) viruses according to the Baltimore Virus Classification. In this study, we summarize the research progresses of host-mediated RNA editing with experimentally validated evidence by grouping viruses into positive-sense single-stranded RNA (+ssRNA), negative-sense single-stranded RNA (-ssRNA), single-stranded RNA reverse transcribing (ssRNA-RT), double-stranded DNA (dsDNA), and double-stranded DNA reverse transcribing (dsDNA-RT), and accordingly delineate a landscape of the involved RNA editing mechanisms (deamination dependent/independent) and molecular effects (proviral/antiviral) between viruses and hosts (Fig. 2).

RNA editing in +ssRNA viruses

+ssRNA viruses infecting cellular hosts rely upon positive-stranded RNA as their primary genetic material [35]. Hitherto, host-mediated RNA editing sites have been documented in several+ssRNA viruses, for instance, enterovirus 71 (EV71) [36–40], hepatitis C virus (HCV) [24, 41–45], and zika virus (ZIKV) [30, 46–50]. In such viruses, both ADARs and APOBECs play important roles in the innate immune response commonly less dependent on deamination (Fig. 3A).

EV71, first described in 1974, is a kind of +ssRNA viruses that belongs to the *Picornaviridae* family, with genome size of about 7.4 kb nucleotides. EV71 can target the human central nervous system and cause

Fig. 2 The landscape of editing mechanisms (deamination dependent/independent) and effects (proviral/antiviral) in viruses with experimental support. All relevant editing enzymes are listed together with the number of supported publications

hand-foot-mouth disease and herpangina, commonly in children under 5 years old [51]. Multiple lines of evidence have shown that APOBEC3G, a host restriction factor of EV71, exerts an antiviral effect by inhibiting virus replication and infectivity without requiring deamination activity [36, 37]. First, the change of key deaminated residues in APOBEC3G (H257R and E259Q in the C-terminal of CD2 domain) does not affect its antiviral effect [36], indicating that the single-stranded RNA-binding domain, but not the deamination activity of APOBEC3G,

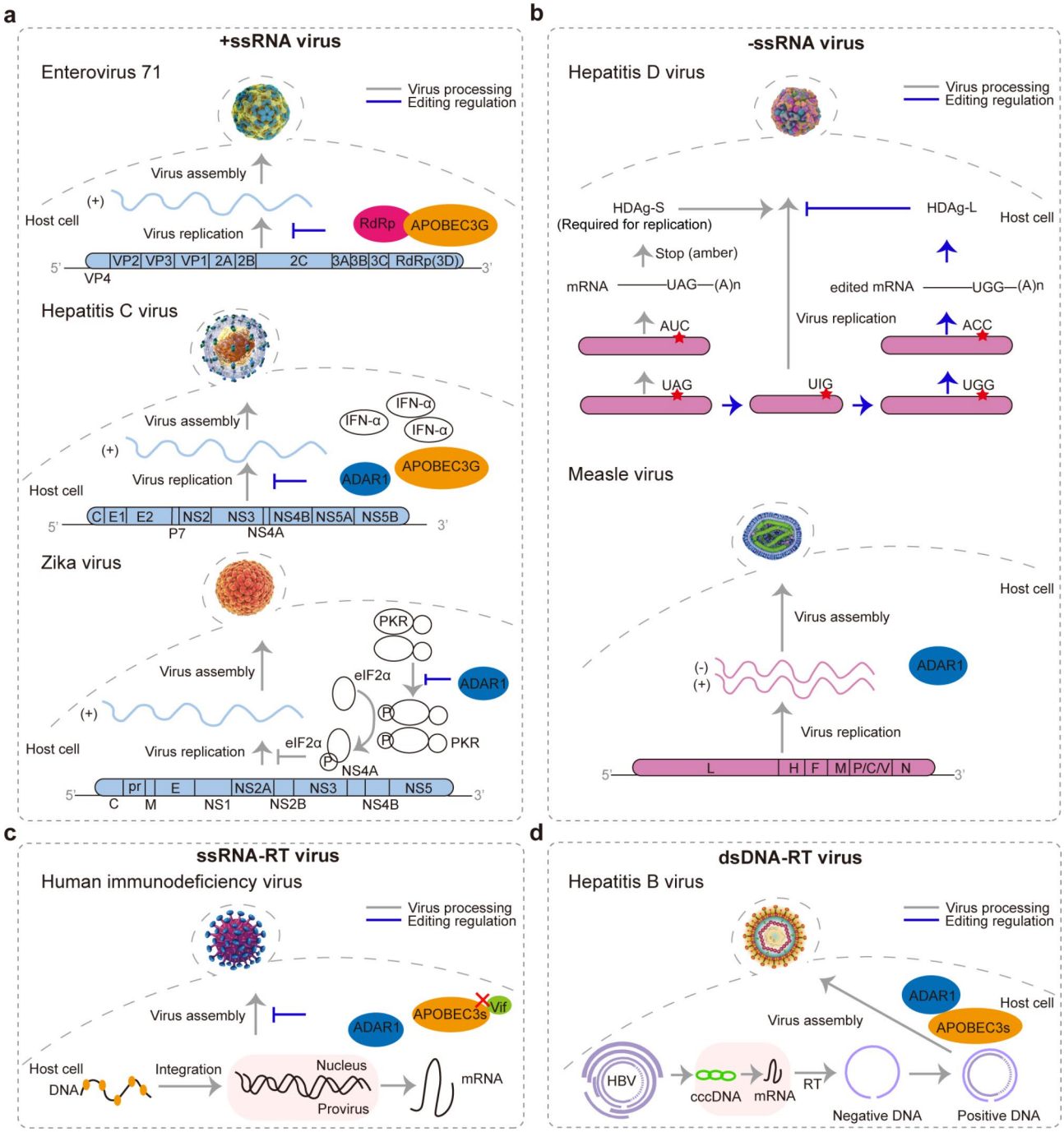

Fig. 3 Biological processes of host-mediated RNA editing in viruses, supported with more than two independent publications. **(a)** RNA editing in + ssRNA virus. **(b)** RNA editing in -ssRNA virus. **(c)** RNA editing in ssRNA-RT virus. **(d)** RNA editing in dsDNA-RT virus

is essential for antiviral effect [37]. Second, although non-structural protein 2C of EV71 can antagonize APOBEC3G's suppression, replication of EV71 is slowed down in APOBEC3G-expressed cells because APOBEC3G could competitively bind to EV71's 5'UTR and accordingly inhibit EV71 protein synthesis [37]. Third, the infectivity of EV71 can also be reduced by APOBEC3G due to its interaction with virus protein 3D (also known as RdRp, assisting the synthesis of EV71) and packaging into progeny virions [36]. Thus, RNA editing acting on EV71 is associated with APOBEC3G in favor of antiviral effect without deamination.

HCV, first isolated in 1989, is a member of the *Flaviviridae* family with genome size of about 9.6 kb nucleotides [52]. It is capable to infect hepatocytes and extrahepatic cells, causing chronic liver disease, cirrhosis,

and even hepatocellular carcinoma [53]. Studies have shown that both ADAR1 and APOBEC3G have antiviral effects on HCV yet through different mechanisms [24, 43, 45]. In detail, ADAR1 is identified as an important contributor to the innate immune response (including dsRNA-dependent protein kinase, PKR, and interferon, such as IFN-α) during HCV life cycle [24], which is supported by the finding that IFN-α may specifically restrain HCV replication through A-to-I editing [45]. Moreover, two polymorphism sites in ADAR1 (viz., rs1127326 and rs2229857) are significantly associated with the outcome of HCV clinical therapy [24] and the depletion of ADAR1 can enhance HCV replication [24]. While, for APOBEC3G, its expression is reported to be elevated in hepatocytes of HCV-infected patients [43] and knockdown experiments revealed its role on the inhibition of HCV replication without hypermutation in the viral genome [44], indicating APOBEC3G's antiviral effect on HCV without requiring deamination.

ZIKV, with genome size of about 10.8 kb nucleotides, was first isolated in 1947 from *rhesus macaque* [54]. As a member of the *Flaviviridae* family, it can be transmitted through blood, placenta, and sex [55], and cause severely abnormal nervous diseases, such as congenital Zika syndrome and Guillain-Barré syndrome in children and adults, which might be explained by one hypothesis that abnormal RNA editing events mediated by host ADAR1 are associated with disease pathogenesis as a role of host immune mechanisms [47]. Different from HCV, host-mediated RNA editing exerts a proviral effect on ZIKV, which is critical to ensuring viral life activities [50]. Specifically, ADAR1 promotes ZIKV replication by preventing the phosphorylation of eIF2α carried out by PKR and IFN during the innate antiviral immune response and by decreasing host cell apoptosis to a certain degree [30]. This proviral effect is mediated by both ADAR1p150 (a full-length interferon-inducible isoform of ADAR1 that mainly localizes to the cytoplasm) and ADAR1p110 (a shorter and constitutively active isoform that resides in the nucleus) [30]. Of note, the deamination activity is unnecessary for this proviral effect since mutations in the deaminase domain of ADAR1p150 and ADAR1p110 do not affect the viral replicon RNA [30].

SARS-CoV-2, as a member of +ssRNA viruses belonging to the *Coronaviridae* family with the largest genome (~30 kb) among RNA viruses, caused the global pandemic due to its highly adaptive genomic variants [56, 57]. Albeit absent from adequate experimental evidence, integrative bioinformatic analysis of large-scale RNA-seq data revealed potential C-to-U and A-to-I conversions mediated by APOBECs and ADARs along the SARS-CoV-2 genome [58–62] (Fig. 4). It has also been reported that both APOBECs and ADARs may function in host immune response pathways to exert different effects on SARS-CoV-2 [63–65] (Fig. 4). Among the APOBECs, AID is the key initiation factor of the host humoral immune response against SARS-CoV-2 [66], while APOBEC1 and APOBEC3A, especially APOBEC3A, are likely to be responsible for C-to-U transformation and make a proviral effect by facilitating replication and propagation

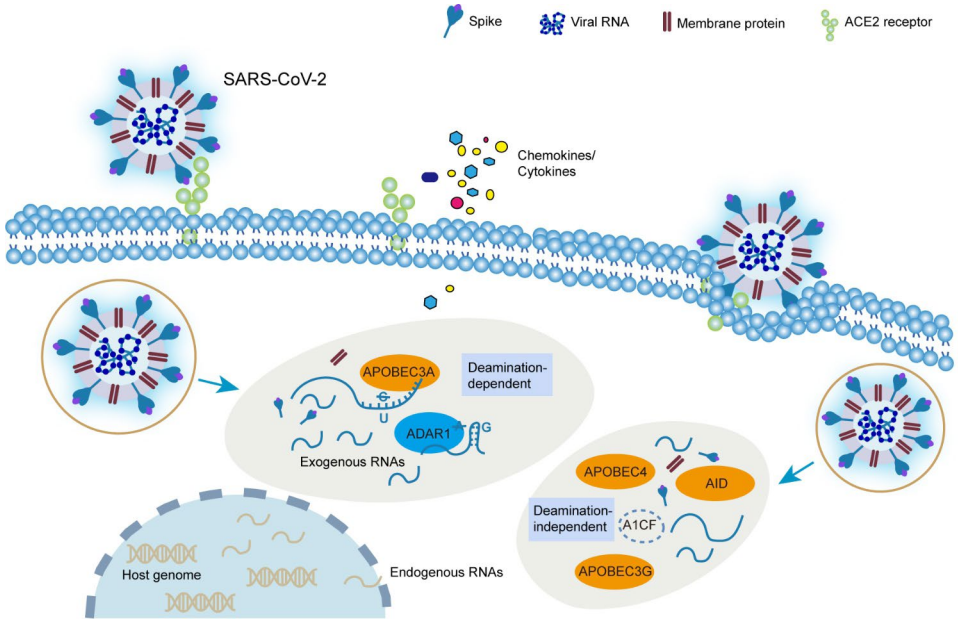

Fig. 4 Schematic overview of the potential role of APOBECs and ADARs in host-mediated RNA editing of SARS-CoV-2. In SARS-CoV-2, both ADAR1 and APOBEC3A are associated with exogenous viral RNAs through deamination-dependent mechanism. By contrast, other members of APOBEC family, such as AID, APOBEC3G, and APOBEC4, together with partners (like A1CF), exert effects through deamination-independent mechanism

of SARS-CoV-2 [67]. Moreover, APOBEC-1 complementation factor (A1CF), a partner of APOBEC1, can interact with SARS-CoV-2 RNAs directly and specifically [68]. In addition, APOBEC4 is up-regulated in patients infected with SARS-CoV-2, causing a host antiviral response [69]. As for the ADAR members, ADAR1 may mediate A-to-I conversion and inhibit SARS-CoV-2 replication [60, 70] with an antiviral effect [62, 71].

RNA editing in -ssRNA viruses

Unlike +ssRNA viruses, the genetic materials of -ssRNA viruses consist of single-stranded RNAs of the negative or antisense strand that do not encode proteins [72]. To date, RNA editing has been found to exert influences on -ssRNA viruses, such as hepatitis D virus (HDV) [19, 21, 73–92] and measles virus (MeV) [93–95] (Fig. 3B). Generally, in contrast to +ssRNA viruses, -ssRNA viruses seem to be more subjected to deamination by ADARs, which have an antiviral effect, especially in HDV.

HDV, belonging to the *Kolmioviridae* family, is a circular-RNA virus of ~1.7 kb nucleotides and its life cycle requires hepatitis B virus (HBV) for assembly and release of HDV particles [75]. Infection of HDV can cause liver diseases, such as chronic or severe hepatitis and cirrhosis. It was revealed that ADAR1 plays a central role in the inhibition of virus replication [19, 90]; ADAR1 could catalyze HDV amber/W editing site, which was first identified as U-to-C [19] and later corrected as A-to-G [90] due to the discovery of HDV circular antigenomic RNA. Due to A-to-G editing on amber/W site, two variants of hepatitis delta antigen (HDAg), namely, HDAg-S and HDAg-L, are produced [80, 96, 97]. Specifically, the original codon "UAG" stops the translation of HDAg and produces HDAg-S that can promote virus replication, whereas the edited codon "UGG" encodes tryptophan and yields HDAg-L that can inhibit virus replication. Thus, ADAR1 provokes an antiviral effect after HDV infection by producing HDAg-L [92]. During this process, ADAR1p110 plays a major role through deamination-dependent activity [85], while ADAR1p150 is responsible for IFN-α stimulation without deamination [83, 84]. Aside from ADAR1, it was proven that the HDV amber/W site can also be catalyzed by ADAR2 but with much lower editing efficiency [21].

MeV, belonging to the *Paramyxoviridae* family with genome size of about 15.9 kb nucleotides, is thought to emerge in the 6th century BCE (Before Common Era) [98]. Infection with MeV can cause measles, resulting in conjunctivitis, koplik spots, and rash [98]. It has been reported that ADAR1, especially ADAR1p150, exhibits a proviral effect by enabling MeV to evade host antiviral immunity and acts as an antiapoptotic host factor during MeV infection without requiring catalytic activity [93]. Further evidence indicates that MeV replication can be restricted in ADAR1^{KO} cells [94] and the damage on the virus caused by the innate immune response is associated with ADAR1 [95].

Aside from HDV and MeV, RNA editing has also been reported in several other –ssRNA viruses, such as influenza A virus (IAV) [99, 100], dengue virus [99], lymphocytic choriomeningitis virus (LCMV) [101], Ebola virus (EBOV) [102], and Marburg virus [102]. It was computationally suggested that host-mediated RNA editing is essential for IAV genome replication and viral protein synthesis [99], exerting a proviral effect by ADAR1p150 to activate the RIG-I (retinoic acid inducible gene I) signaling pathway without deamination [100]. It was also found in dengue virus, in which ADAR1 enhances virus replication by promoting non-structural protein synthesis [99]. Similarly, infection of LCMV upregulates ADAR1 expression and induces A-to-G mutations, which ultimately inhibit viral protein function and infectivity [101]. Moreover, EBOV and Marburg virus can be modulated by ADAR1 through A-to-I transversion in 3'-UTR, which results in negative regulation of virus translation [102].

RNA editing in ssRNA-RT viruses

ssRNA-RT viruses can establish infection through integrating a DNA copy of the viral genome into host cell chromosome [103]. Till now, studies have discovered that several ssRNA-RT viruses are subjected to host-mediated RNA editing by ADAR1 and APOBECs through deamination-dependent/independent activity [14, 15, 25, 34, 104–123] (Fig. 3C).

Human immunodeficiency virus (HIV), first isolated in 1983 from human, is an enveloped RNA retrovirus with genome size of about 9.2 kb nucleotides [124] that can render acquired immune deficiency syndrome (AIDS). Both ADARs and APOBECs are involved in the host-mediated RNA editing on HIV (including HIV-1 and HIV-2) [108, 121, 122]. On the one hand, ADAR1 affects HIV in a proviral manner by deaminating adenosines [104–108, 120] in the 5'-UTR to stimulate viral infection [108], interacting with PKR to promote virus replication during infection of lymphocytes [120], and enhancing the expression of VP24 (one of HIV proteins) [107]. On the other hand, ADAR1 can also act as an antiviral factor inhibiting viral infectivity and protein synthesis [105]. Unlike the dual effects of ADAR1, APOBEC3s, including APOBEC3A [111], APOBEC3F [112], APOBEC3G [116], and APOBEC3H [116], are mainly involved in inhibiting the replication of both HIV-1 and HIV-2 [121, 122]. Among them, APOBEC3G is well studied to be able to interact with HIV-1 reverse transcriptase and inhibit HIV-1 replication without deamination [34, 125]. Strikingly, to antagonize the inhibition of APOBEC3G, the virion infectivity factor (vif) of HIV [25], a viral accessory

protein, has been proven to interact directly with APOBEC3G [115] and prevent packaging of APOBEC3G into virion [123].

In addition to HIV, other ssRNA-RT viruses, albeit with limited experimental evidence, are also reported to be affected by host-mediated RNA editing through APOBEC3s and ADARs. It is indicated that life activity of caprine arthritis encephalitis virus (CAEV), feline immunodeficiency virus (FIV), murine leukemia virus (MLV), mouse mammary tumor virus (MMTV), and porcine endogenous retrovirus (PER) can be antagonized by host-mediated RNA editing (with or without requiring deamination), potentially owing to degradation of APOBEC3s by vif protein [15, 113, 114, 118, 119]. Specifically, in CAEV [113] and FIV [114], just like HIV, the antiviral effect of APOBEC3s can be counteracted by vif protein, glycosylated Gag (glyco-Gag) protein in MLV could protect the reverse transcription complex from APOBEC3s' antagonization [119], and the reverse transcription and replication of MMTV and PER replicon RNAs can be inhibited by APOBEC3s through deamination activity [15, 118]. Different from APOBEC3s, ADAR1 mainly makes proviral effects on equine infectious anemia virus (EIAV), simian T-cell leukemia virus (STLV), and human T-cell leukemia virus (HTLV) [14, 109, 110]. It was reported that ADAR1 contributes to the adaptation of EIAV [14] and STLV [110] by increasing A-to-G editing level through deamination. Moreover, ADAR1 also promotes HTLV replication by inhibiting the host PKR activity without requiring deamination [109].

RNA editing in dsDNA viruses

In addition to RNA viruses, dsDNA viruses, such as BK polyomavirus (BKPyV), Epstein-Barr virus (EBV), human cytomegalovirus (HHV), human papillomaviruses (HPV), and herpes simplex virus (HSV), have been reported to be targeted and impacted by host-mediated RNA editing, in which APOBECs are the main mediators [126–131]. For example, APOBEC3B, regarded as an innate immune DNA cytosine deaminase sensor, is upregulated after infection of both BKPyV and EBV, thereby activating host innate immunity against viruses [126, 127]. In BKPyV, APOBEC3B is influenced by virus large T antigen, leading to the activation of immune factors like interferon-stimulated genes [126, 127]. In EBV, knockdown of BORF2, the large subunit of the viral ribonucleotide reductase, can activate APOBEC3B and further cause lower viral load, infectivity, and hypermutation [126, 127]. Moreover, it was revealed that APOBEC3G also plays an antiviral effect on HHV [129] and HPV [128] by inhibiting virus infection. Aside from APOBEC3s, APOBEC1 might also exert an antiviral effect with deamination that further reduces virus replication on HSV [130]. Remarkably, C-to-T transitions on HSV *UL54* gene through APOBEC1 deamination activity are essential impaired accumulation of HSV DNA copy numbers and mRNA transcripts [130].

To be specific, studies have documented that host-mediated RNA editing influences viral load of HPV [128, 131] that is the chief culprit of cervical cancer. APOBECs, especially APOBEC3A and APOBEC3G, participate in regulating cell viability [128, 131]. In detail, APOBEC3A exerts an antiviral effect caused by C-to-T transitions of HPV *E6* gene [131]. Consistently, it was also reported that knockdown of APOBEC3A or APOBEC3G reduces the frequency of A+T in *E2* gene of HPV [128]. In total, APOBECs are inclined to play important roles in host-mediated RNA editing by deamination-dependent activity in dsDNA viruses.

RNA editing in dsDNA-RT viruses

dsDNA-RT viruses, albeit well studied with respect to innate immunity [132], have limited evidence in host-mediated RNA editing [133]. HBV, with a genome size of about 3.2 kb nucleotides, is the first human hepatitis virus from which the proteins and genome could be identified and characterized [134]. In human, HBV infection can cause acute and chronic liver diseases, including cirrhosis and hepatocellular carcinoma [134], which are related with immunomodulatory factors, such as APOBECs, to induce innate and adaptive immune responses [135].

Evidence has shown that APOBECs can influence HBV replication by complex host-mediated RNA editing mechanisms (Fig. 3D). First, reverse transcription, a part of dsDNA-RT viral replication process, is inhibited by APOBEC3B through deamination [136–138]. In addition, RNA binding proteins, like DHX9, can reduce the antiviral effect of APOBEC3B as co-factors [136–138]. Second, APOBEC3C, APOBEC3G, and APOBEC3H also contribute to the innate anti-HBV immune response in host [139, 140]; in human liver, the three catalytic proteins inhibit HBV viral replication by hypermutation of DNA sequences [139, 140]. On the contrary, APOBEC3F exerts deamination-independent activity through IFN-α release and is also involved in HBV replication [141]. Notably, APOBEC3G inhibits HBV replication, especially interference of reverse transcription by deamination-dependent activity [142–144]. Meanwhile, it also inhibits HBV reverse transcription without deamination, targets viral DNA-RNA hybrids [145] and is involved in the innate antiviral immune response [146].

Concluding remarks & perspectives

Through synthesizing the current knowledge of host-mediated RNA editing in a variety of viruses, it is clearly shown that RNA editing can induce proviral or antiviral effects by promoting or inhibiting virus replication,

protein synthesis and/or infectivity with or without requiring deamination. According to the synthesized knowledge, deamination-dependent RNA editing is mainly found in -ssRNA viruses, whereas deamination-independent regulation is observed in the majority of +ssRNA viruses, indicating their divergence in RNA editing mechanisms. This is presumably due to the difference in viral replication mechanism and life cycle, as the genetic materials of +ssRNA viruses could be translated as mRNA, while -ssRNA viruses need additional steps for transcription/reverse transcription [72, 103]. Specifically, during the additional steps, complementary RNAs of -ssRNA viruses are transcribed as intermediates, forming dsRNA substrates that may be easier to be edited directly by ADAR1. Moreover, the preference of deamination-dependent/independent RNA editing mechanism may be also related to viral transmission routes. Deamination-independent mechanism prefers respiratory and digestive systems for virus transmission, whereas deamination-dependent mechanism prefers blood system transmission. Furthermore, different classes of viruses present differences and similarities in terms of host-mediated RNA editing (Fig. 2). Noticeably, RNA viruses prefer to employ both ADARs and APOBECs, whereas DNA viruses tend to use APOBECs only, which will be enriched, updated, and evolved with future related studies. APOBECs, particularly APOBEC3G, exert antiviral effects in nearly all viruses except -ssRNA viruses, while ADARs participate in nearly all viruses except dsDNA viruses. In addition, many other characteristics, such as hosts [14] and virus toxicity [32], may be also associated with RNA editing mechanisms. Collectively, these results indicate the diversity of RNA editing between hosts and viruses, yet requiring more experimental investigations to decipher complex underlying mechanisms.

As also indicated in this report, host endogenous RNAs and exogenous viral RNAs could be distinguished by differential editing patterns mediated by ADAR enzymes [147]. Endogenous RNAs are appropriately edited, while invasive exogenous viral RNAs are edited at low levels upon infection. High abundance of lowly edited viral RNAs with dsRNAs could lead to the activation of dsRNA sensor (MDA5) and subsequent antiviral interferon response pathway [148]. Thus, aberrant RNA editing in viral RNAs may be beneficial to the immune escape of virus, due to the loss of capability of host cell to discriminate endogenous RNAs from exogenous viral RNAs [147].

Host-mediated RNA editing, albeit relatively weak in viruses, may be an important contributor to virus evolution [149]. It has been found that viruses can reduce toxicity, enhance infectivity, and speed up replication by changing viral core genetic sequences through host-mediated RNA editing mechanisms [21, 73]. It is believed that RNA editing events in different virus clades might be under differential evolutionary selection and contribute to viral phenotypic diversity [57]. Moreover, specific non-synonymous editing sites, like amber/W site in HDV, are considered as critical events provoking proviral or antiviral effects [90]. Thus, host-mediated RNA editing may act as a cradle to foster the adaptive evolution of virus, which is yet heterogenous in different classes of viruses. One hypothesis is that deamination-dependent activity contributes to the adaptive evolution of -ssRNA viruses, which needs to be further investigated, both computationally and experimentally.

Undoubtedly, existing studies on RNA editing in viruses have limitations. RNA editing sites in viruses can be missed or miscalculated due to low sequencing coverage, sequencing error or/and short read length. Specifically, as multiple RNA editing sites may be co-edited and exert complex effects, it is challenging to identify/verify the coexistence of adjacent RNA editing sites based on short sequencing reads, especially for exogenous RNAs. In the future, long reads generated by the third-generation sequencing technology have great potential to capture a complete picture of RNA editing sites and to detect cooperativity among RNA editing sites during dynamic viral life cycles.

In addition, given the ongoing pandemic of COVID-19, it would be desirable to conduct a SARS-CoV-2 cohort study to systematically investigate the host-mediated RNA editing mechanisms and molecular effects on SARS-CoV-2 and further explore the editing heterogeneity among infected people with mild, moderate and severe symptoms. Notably, a model of RNA editing on SARS-CoV-2 transcriptome was proposed [65]; although this model explains differential editing frequencies and patterns before and after viral replication on positive- and negative-sense viral transcripts, it cannot elucidate diverse effects of RNA editing on SARS-CoV-2 in patients with different symptoms.

Taken together, our study delineates the landscape of RNA editing-associated mechanisms and effects in different classes of viruses, which would provide potentially valuable insights and also call on worldwide collaborative efforts, particularly during the pandemic caused by SARS-CoV-2 as well as monkeypox virus, for better understanding the host-mediated RNA editing on both ever-reported and newly-emerging viruses.

Acknowledgements
We thank Prof. Jun Yu for constructive suggestions. We also thank a number of partners for providing suggestions as well as anonymous reviewers for their valuable comments on this work.

Authors' contributions
ZZ and LLH conceived the concept, TTZ, GYN, YSZ and MC researched the literature, TTZ and GYN plotted the figures, and TTZ drafted the manuscript

with input from GYN, YSZ, CYL. ZZ and LLH revised the manuscript and supervised the work. All authors read and approved the manuscript.

Funding
Special Investigation on Science and Technology Basic Resources of the MOST [2019FY100102]; The Youth Innovation Promotion Association of Chinese Academy of Sciences [2018134]; Strategic Priority Research Program of the Chinese Academy of Sciences [XDA19050302, XDB38030200, XDB38030400]; National Natural Science Foundation of China [32030021, 31871328]; International Partnership Program of the Chinese Academy of Sciences [153F11KYSB20160008]; the Open Biodiversity and Health Big Data Programme of IUBS.

Data availability
Not applicable.

Declarations

Competing interests
The authors declare no competing interests.

Received: 27 February 2023 / Accepted: 17 March 2023
Published online: 28 March 2023

References

1. Nishikura K. Functions and regulation of RNA editing by ADAR deaminases. Annu Rev Biochem. 2010;79:321–49.
2. Behm M, Ohman M. RNA editing: a contributor to neuronal dynamics in the mammalian brain. Trends Genet. 2016;32(3):165–75.
3. Picardi E, Manzari C, Mastropasqua F, Aiello I, D'Erchia AM, Pesole G. Profiling RNA editing in human tissues: towards the inosinome Atlas. Sci Rep. 2015;5:14941.
4. Tan MH, Li Q, Shanmugam R, Piskol R, Kohler J, Young AN, et al. Dynamic landscape and regulation of RNA editing in mammals. Nature. 2017;550(7675):249–54.
5. Small ID, Schallenberg-Rudinger M, Takenaka M, Mireau H, Ostersetzer-Biran O. Plant organellar RNA editing: what 30 years of research has revealed. Plant J. 2020;101(5):1040–56.
6. Li M, Xia L, Zhang Y, Niu G, Li M, Wang P, et al. Plant editosome database: a curated database of RNA editosome in plants. Nucleic Acids Res. 2019;47(D1):D170–D4.
7. Wahlstedt H, Daniel C, Enstero M, Ohman M. Large-scale mRNA sequencing determines global regulation of RNA editing during brain development. Genome Res. 2009;19(6):978–86.
8. Han L, Diao L, Yu S, Xu X, Li J, Zhang R, et al. The genomic landscape and clinical relevance of A-to-I RNA editing in human cancers. Cancer Cell. 2015;28(4):515–28.
9. Chan TW, Fu T, Bahn JH, Jun HI, Lee JH, Quinones-Valdez G, et al. RNA editing in cancer impacts mRNA abundance in immune response pathways. Genome Biol. 2020;21(1):268.
10. Nishikura K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat Rev Mol Cell Biol. 2016;17(2):83–96.
11. Deng P, Khan A, Jacobson D, Sambrani N, McGurk L, Li X, et al. Adar RNA editing-dependent and -independent effects are required for brain and innate immune functions in Drosophila. Nat Commun. 2020;11(1):1580.
12. Merkle T, Merz S, Reautschnig P, Blaha A, Li Q, Vogel P, et al. Precise RNA editing by recruiting endogenous ADARs with antisense oligonucleotides. Nat Biotechnol. 2019;37(2):133–8.
13. Eisenberg E, Levanon EY, A-to-I. RNA editing - immune protector and transcriptome diversifier. Nat Rev Genet. 2018;19(8):473–90.
14. Tang YD, Zhang X, Na L, Wang XF, Fu LH, Zhu CH, et al. Double-stranded-RNA-specific adenosine deaminase 1 (ADAR1) is proposed to contribute to the adaptation of equine infectious anemia virus from horses to donkeys. Arch Virol. 2016;161(10):2667–72.
15. Jin SY, Choi HY, Kim HS, Jung YT. Human-APOBEC3G-dependent restriction of porcine endogenous retrovirus replication is mediated by cytidine deamination and inhibition of DNA strand transfer during reverse transcription. Arch Virol. 2018;163(7):1907–14.
16. Matthews MM, Thomas JM, Zheng Y, Tran K, Phelps KJ, Scott AI, et al. Structures of human ADAR2 bound to dsRNA reveal base-flipping mechanism and basis for site selectivity. Nat Struct Mol Biol. 2016;23(5):426–33.
17. Smith HC. RNA binding to APOBEC deaminases; not simply a substrate for C to U editing. RNA Biol. 2017;14(9):1153–65.
18. Zhang Q, Xiao X. Genome sequence-independent identification of RNA editing sites. Nat Methods. 2015;12(4):347–50.
19. Casey JL, Bergmann KF, Brown TL, Gerin JL. Structural requirements for RNA editing in hepatitis delta virus: evidence for a uridine-to-cytidine editing mechanism. Proc Natl Acad Sci U S A. 1992;89(15):7149–53.
20. Niu G, Zou D, Li M, Zhang Y, Sang J, Xia L, et al. Editome Disease Knowledgebase (EDK): a curated knowledgebase of editome-disease associations in human. Nucleic Acids Res. 2019;47(D1):D78–D83.
21. Jayan GC, Casey JL. Increased RNA editing and inhibition of hepatitis delta virus replication by high-level expression of ADAR1 and ADAR2. J Virol. 2002;76(8):3819–27.
22. Samuel CE. RNA editing minireview series. J Biol Chem. 2003;278(3):1389–90.
23. Sanjuan R, Domingo-Calap P. Mechanisms of viral mutation. Cell Mol Life Sci. 2016;73(23):4433–48.
24. Pujantell M, Franco S, Galvan-Femenia I, Badia R, Castellvi M, Garcia-Vidal E, et al. ADAR1 affects HCV infection by modulating innate immune response. Antiviral Res. 2018;156:116–27.
25. Bertine M, Charpentier C, Visseaux B, Storto A, Collin G, Larrouy L, et al. High level of APOBEC3F/3G editing in HIV-2 DNA vif and pol sequences from antiretroviral-naive patients. AIDS. 2015;29(7):779–84.
26. Burnett A, Spearman P. APOBEC3G multimers are recruited to the plasma membrane for packaging into human immunodeficiency virus type 1 virus-like particles in an RNA-dependent process requiring the NC basic linker. J Virol. 2007;81(10):5000–13.
27. Casey JL, Gerin JL. Hepatitis D virus RNA editing: specific modification of adenosine in the antigenomic RNA. J Virol. 1995;69(12):7593–600.
28. Ratcliff J, Simmonds P. Potential APOBEC-mediated RNA editing of the genomes of SARS-CoV-2 and other coronaviruses and its impact on their longer term evolution. Virology. 2021;556:62–72.
29. Samuel CE. Adenosine deaminases acting on RNA (ADARs) are both antiviral and proviral. Virology. 2011;411(2):180–93.
30. Zhou S, Yang C, Zhao F, Huang Y, Lin Y, Huang C, et al. Double-stranded RNA deaminase ADAR1 promotes the Zika virus replication by inhibiting the activation of protein kinase PKR. J Biol Chem. 2019;294(48):18168–80.
31. Muriaux D, Darlix JL. Properties and functions of the nucleocapsid protein in virus assembly. RNA Biol. 2010;7(6):744–53.
32. Volchkova VA, Dolnik O, Martinez MJ, Reynard O, Volchkov VE. RNA editing of the GP Gene of Ebola Virus is an important pathogenicity factor. J Infect Dis. 2015;212(Suppl 2suppl 2):226–33.
33. Fehrholz M, Kendl S, Prifert C, Weissbrich B, Lemon K, Rennick L, et al. The innate antiviral factor APOBEC3G targets replication of measles, mumps and respiratory syncytial viruses. J Gen Virol. 2012;93(Pt 3):565–76.
34. Li XY, Guo F, Zhang L, Kleiman L, Cen S. APOBEC3G inhibits DNA strand transfer during HIV-1 reverse transcription. J Biol Chem. 2007;282(44):32065–74.
35. Kockler ZW, Gordenin DA. From RNA world to SARS-CoV-2: the edited story of RNA viral evolution. Cells. 2021;10(6):1557.
36. Wang H, Zhong M, Li Y, Li K, Wu S, Guo T, et al. APOBEC3G is a restriction factor of EV71 and mediator of IMB-Z antiviral activity. Antiviral Res. 2019;165:23–33.
37. Li Z, Ning S, Su X, Liu X, Wang H, Liu Y, et al. Enterovirus 71 antagonizes the inhibition of the host intrinsic antiviral factor A3G. Nucleic Acids Res. 2018;46(21):11514–27.
38. You L, Chen J, Liu W, Xiang Q, Luo Z, Wang W, et al. Enterovirus 71 induces neural cell apoptosis and autophagy through promoting ACOX1 downregulation and ROS generation. Virulence. 2020;11(1):537–53.
39. Wang LC, Chen SO, Chang SP, Lee YP, Yu CK, Chen CL, et al. Enterovirus 71 proteins 2A and 3D antagonize the antiviral activity of Gamma Interferon via Signaling Attenuation. J Virol. 2015;89(14):7028–37.
40. Ji XY, Wang HQ, Hao LH, He WY, Gao RM, Li YP, et al. Synthesis and antiviral activity of N-phenylbenzamide derivatives, a novel class of enterovirus 71 inhibitors. Molecules. 2013;18(3):3630–40.
41. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):45–57.
42. Ferreira AR, Magalhaes AC, Camoes F, Gouveia A, Vieira M, Kagan JC, et al. Hepatitis C virus NS3-4A inhibits the peroxisomal MAVS-dependent antiviral signalling response. J Cell Mol Med. 2016;20(4):750–7.

43. Komohara Y, Yano H, Shichijo S, Shimotohno K, Itoh K, Yamada A. High expression of APOBEC3G in patients infected with hepatitis C virus. J Mol Histol. 2006;37(8–9):327–32.
44. Peng ZG, Zhao ZY, Li YP, Wang YP, Hao LH, Fan B, et al. Host apolipoprotein B messenger RNA-editing enzyme catalytic polypeptide-like 3G is an innate defensive factor and drug target against hepatitis C virus. Hepatology. 2011;53(4):1080–9.
45. Taylor DR, Puig M, Darnell ME, Mihalik K, Feinstone SM. New antiviral pathway that mediates hepatitis C virus replicon interferon sensitivity through ADAR1. J Virol. 2005;79(10):6291–8.
46. McGrath EL, Rossi SL, Gao J, Widen SG, Grant AC, Dunn TJ, et al. Differential responses of human fetal brain neural stem cells to Zika Virus infection. Stem Cell Reports. 2017;8(3):715–27.
47. Piontkivska H, Plonski NM, Miyamoto MM, Wayne ML. Explaining pathogenicity of congenital Zika and Guillain-Barre Syndromes: does Dysregulation of RNA editing play a role? BioEssays. 2019;41(6):e1800239.
48. Babitha Suseelan Bhargavi AM. Global outbreaks of zika infection by epidemic observatory.Global Biosecurity. 2020;4(1).
49. Khrustalev VV, Khrustaleva TA, Sharma N, Giri R. Mutational pressure in Zika Virus: local ADAR-editing areas associated with pauses in translation and replication. Front Cell Infect Microbiol. 2017;7:44.
50. Piontkivska H, Frederick M, Miyamoto MM, Wayne ML. RNA editing by the host ADAR system affects the molecular evolution of the Zika virus. Ecol Evol. 2017;7(12):4475–85.
51. Lee TC, Guo HR, Su HJ, Yang YC, Chang HL, Chen KT. Diseases caused by enterovirus 71 infection. Pediatr Infect Dis J. 2009;28(10):904–10.
52. Hossein Keyvani MF. Seyed Hamid Reza Monavari, Hamid Reza Mollaie. Hepatitis C virus–proteins, diagnosis, treatment and new approaches for vaccine development. APJCP. 2012;13(12):5931–49.
53. Pol S, Vallet-Pichard A, Hermine O. Extrahepatic cancers and chronic HCV infection. Nat Rev Gastroenterol Hepatol. 2018;15(5):283–90.
54. Wang A, Thurmond S, Islas L, Hui K, Hai R. Zika virus genome biology and molecular pathogenesis. Emerg Microbes Infect. 2017;6(3):e13.
55. Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev. 2016;29(3):487–524.
56. Song S, Ma L, Zou D, Tian D, Li C, Zhu J, et al. The global landscape of SARS-CoV-2 genomes, variants, and haplotypes in 2019nCoVR. Genomics Proteom Bioinf. 2020;18(6):749–59.
57. Teng X, Li Q, Li Z, Zhang Y, Niu G, Xiao J, et al. Compositional variability and mutation spectra of monophyletic SARS-CoV-2 clades. Genomics Proteom Bioinf. 2020;18(6):648–63.
58. Simmonds P. Rampant C–>U hypermutation in the genomes of SARS-CoV-2 and other coronaviruses: causes and consequences for their short- and long-term evolutionary trajectories. mSphere. 2020;5(3):e00408–20.
59. Simmonds P, Ansari MA. Extensive C->U transition biases in the genomes of a wide range of mammalian RNA viruses; potential associations with transcriptional mutations, damage- or host-mediated editing of viral RNA. PLoS Pathog. 2021;17(6):e1009596.
60. Peng X, Luo Y, Li H, Guo X, Chen H, Ji X, et al. RNA editing increases the nucleotide diversity of SARS-CoV-2 in human host cells. PLoS Genet. 2022;18(3):e1010130.
61. Song Y, He X, Yang W, Wu Y, Cui J, Tang T, et al. Virus-specific editing identification approach reveals the landscape of A-to-I editing and its impacts on SARS-CoV-2 characteristics and evolution. Nucleic Acids Res. 2022;50(5):2509–21.
62. Picardi E, Mansi L, Pesole G. Detection of A-to-I RNA editing in SARS-COV-2. Genes (Basel). 2021;13(1):41.
63. Mourier T, Sadykov M, Carr MJ, Gonzalez G, Hall WW, Pain A. Host-directed editing of the SARS-CoV-2 genome. Biochem Biophys Res Commun. 2021;538:35–9.
64. Azgari C, Kilinc Z, Turhan B, Circi D, Adebali O. The mutation profile of SARS-CoV-2 is primarily shaped by the host antiviral defense. Viruses. 2021;13(3):394.
65. Gabriella M. Evidence for host-dependent RNA editing in the transcriptome of SARS-CoV-2.Science Advances. 2020(6):eabb5813.
66. Ullah A, Mabood N, Maqbool M, Khan L, Ullah M. Cytidine deamination-induced perpetual immunity to SAR-CoV-2 infection is a potential new therapeutic target. Int J Med Sci. 2021;18(16):3788–93.
67. Kim K, Calabrese P, Wang S, Qin C, Rao Y, Feng P et al. The roles of APOBEC-mediated RNA editing in SARS-CoV-2 mutations, replication and fitness. bioRxiv. 2022.
68. Schmidt N, Lareau CA, Keshishian H, Ganskih S, Schneider C, Hennig T, et al. The SARS-CoV-2 RNA-protein interactome in infected human cells. Nat Microbiol. 2021;6(3):339–53.
69. Meshcheryakova A, Pietschmann P, Zimmermann P, Rogozin IB, Mechtcheriakova D. AID and APOBECs as multifaceted intrinsic virus-restricting factors: emerging concepts in the light of COVID-19. Front Immunol. 2021;12:690416.
70. Vlachogiannis NI, Verrou KM, Stellos K, Sfikakis PP, Paraskevis D. The role of A-to-I RNA editing in infections by RNA viruses: possible implications for SARS-CoV-2 infection. Clin Immunol. 2021;226:108699.
71. Gregori J, Cortese MF, Pinana M, Campos C, Garcia-Cehic D, Andres C, et al. Host-dependent editing of SARS-CoV-2 in COVID-19 patients. Emerg Microbes Infect. 2021;10(1):1777–89.
72. Ortin J, Martin-Benito J. The RNA synthesis machinery of negative-stranded RNA viruses.Virology. 2015;479–480:532 – 44.
73. Linnstaedt SD, Kasprzak WK, Shapiro BA, Casey JL. The fraction of RNA that folds into the correct branched secondary structure determines hepatitis delta virus type 3 RNA editing levels. RNA. 2009;15(6):1177–87.
74. Sato S, Cornillez-Ty C, Lazinski DW. By inhibiting replication, the large hepatitis delta antigen can indirectly regulate amber/W editing and its own expression. J Virol. 2004;78(15):8120–34.
75. Casey JL. Control of ADAR1 editing of hepatitis delta virus RNAs. Curr Top Microbiol Immunol. 2012;353:123–43.
76. Casey JL, Bergmann KF, Brown TL, Gerin JL. Determinants of RNA editing in hepatitis delta virus. Prog Clin Biol Res. 1993;382:5–11.
77. Cheng Q, Jayan GC, Casey JL. Differential inhibition of RNA editing in hepatitis delta virus genotype III by the short and long forms of hepatitis delta antigen. J Virol. 2003;77(14):7786–95.
78. Zheng H, Fu TB, Lazinski D, Taylor J. Editing on the genomic RNA of human hepatitis delta virus. J Virol. 1992;66(8):4693–7.
79. Jayan GC, Casey JL. Effects of conserved RNA secondary structures on hepatitis delta virus genotype I RNA editing, replication, and virus production. J Virol. 2005;79(17):11187–93.
80. Shih KN, Chuang YT, Liu H, Lo SJ. Hepatitis D virus RNA editing is inhibited by a GFP fusion protein containing a C-terminally deleted delta antigen. J Gen Virol. 2004;85(Pt 4):947–57.
81. Wu TT, Bichko VV, Ryu WS, Lemon SM, Taylor JM. Hepatitis delta virus mutant: effect on RNA editing. J Virol. 1995;69(11):7226–31.
82. Jayan GC, Casey JL. Inhibition of hepatitis delta virus RNA editing by short inhibitory RNA-mediated knockdown of ADAR1 but not ADAR2 expression. J Virol. 2002;76(23):12399–404.
83. Hartwig D, Schoeneich L, Greeve J, Schutte C, Dorn I, Kirchner H, et al. Interferon-alpha stimulation of liver cells enhances hepatitis delta virus RNA editing in early infection. J Hepatol. 2004;41(4):667–72.
84. Hartwig D, Schutte C, Warnecke J, Dorn I, Hennig H, Kirchner H, et al. The large form of ADAR 1 is responsible for enhanced hepatitis delta virus RNA editing in interferon-alpha-stimulated host cells. J Viral Hepat. 2006;13(3):150–7.
85. Wong SK, Lazinski DW. Replicating hepatitis delta virus RNA is edited in the nucleus by the small form of ADAR1. Proc Natl Acad Sci U S A. 2002;99(23):15118–23.
86. Greeve J, Hartwig D, Windler E, Greten H. Requirements for editing in the genomic RNA of hepatitis delta virus. Biochimie. 1994;76(12):1209–16.
87. Chen R, Linnstaedt SD, Casey JL. RNA editing and its control in hepatitis delta virus replication. Viruses. 2010;2(1):131–46.
88. Casey JL. RNA editing in hepatitis delta virus genotype III requires a branched double-hairpin RNA structure. J Virol. 2002;76(15):7385–97.
89. Jayan GC. RNA editing in hepatitis delta virus: unsolved puzzles. ScientificWorldJournal. 2004;4:628–37.
90. Polson AG, Bass BL, Casey JL. RNA editing of hepatitis delta virus antigenome by dsRNA-adenosine deaminase. Nature. 1996;380(6573):454–6.
91. Linnstaedt SD, Kasprzak WK, Shapiro BA, Casey JL. The role of a metastable RNA secondary structure in hepatitis delta virus genotype III RNA editing. RNA. 2006;12(8):1521–33.
92. Hsu CW, Juang HH, Kuo CY, Li HP, Iang SB, Lin SH, et al. Structural pattern differences in unbranched rod-like RNA of Hepatitis Delta virus affect RNA editing. Viruses. 2019;11(10):934.
93. Toth AM, Li Z, Cattaneo R, Samuel CE. RNA-specific adenosine deaminase ADAR1 suppresses measles virus-induced apoptosis and activation of protein kinase PKR. J Biol Chem. 2009;284(43):29350–6.
94. Pfaller CK, Donohue RC, Nersisyan S, Brodsky L, Cattaneo R. Extensive editing of cellular and viral double-stranded RNA structures accounts for innate

immunity suppression and the proviral activity of ADAR1p150. PLoS Biol. 2018;16(11):e2006577.
95. Pfaller CK, Radeke MJ, Cattaneo R, Samuel CE. Measles virus C protein impairs production of defective copyback double-stranded viral RNA and activation of protein kinase R. J Virol. 2014;88(1):456–68.
96. Polson AG, Ley HL 3rd, Bass BL, Casey JL. Hepatitis delta virus RNA editing is highly specific for the amber/W site and is suppressed by hepatitis delta antigen. Mol Cell Biol. 1998;18(4):1919–26.
97. Macnaughton TB, Li YI, Doughty AL, Lai MM. Hepatitis delta virus RNA encoding the large delta antigen cannot sustain replication due to rapid accumulation of mutations associated with RNA editing. J Virol. 2003;77(22):12048–56.
98. Dux A, Lequime S, Patrono LV, Vrancken B, Boral S, Gogarten JF, et al. Measles virus and rinderpest virus divergence dated to the sixth century BCE. Science. 2020;368(6497):1367–70.
99. de Chassey B, Aublin-Gex A, Ruggieri A, Meyniel-Schicklin L, Pradezynski F, Davoust N, et al. The interactomes of influenza virus NS1 and NS2 proteins identify new host factors and provide insights for ADAR1 playing a supportive role in virus replication. PLoS Pathog. 2013;9(7):e1003440.
100. Vogel OA, Han J, Liang CY, Manicassamy S, Perez JT, Manicassamy B. The p150 isoform of ADAR1 blocks sustained RLR signaling and apoptosis during influenza virus infection. PLoS Pathog. 2020;16(9):e1008842.
101. Zahn RC, Schelp I, Utermohlen O, von Laer D. A-to-G hypermutation in the genome of lymphocytic choriomeningitis virus. J Virol. 2007;81(2):457–64.
102. Khadka S, Williams CG, Sweeney-Gibbons J, Basler CF. Marburg and Ebola Virus mRNA 3' untranslated regions contain negative regulators of translation that are modulated by ADAR1 editing. J Virol. 2021;95(19):e0065221.
103. Maertens GN, Engelman AN, Cherepanov P. Structure and function of retroviral integrase. Nat Rev Microbiol. 2022;20(1):20–34.
104. Cuadrado E, Booiman T, van Hamme JL, Jansen MH, van Dort KA, Vanderver A, et al. ADAR1 facilitates HIV-1 replication in primary CD4 + T cells. PLoS ONE. 2015;10(12):e0143613.
105. Biswas N, Wang T, Ding M, Tumne A, Chen Y, Wang Q, et al. ADAR1 is a novel multi targeted anti-HIV-1 cellular protein. Virology. 2012;422(2):265–77.
106. Weiden MD, Hoshino S, Levy DN, Li Y, Kumar R, Burke SA, et al. Adenosine deaminase acting on RNA-1 (ADAR1) inhibits HIV-1 replication in human alveolar macrophages. PLoS ONE. 2014;9(10):e108476.
107. Phuphuakrat A, Kraiwong R, Boonarkart C, Lauhakirti D, Lee TH, Auewarakul P. Double-stranded RNA adenosine deaminases enhance expression of human immunodeficiency virus type 1 proteins. J Virol. 2008;82(21):10864–72.
108. Doria M, Neri F, Gallo A, Farace MG, Michienzi A. Editing of HIV-1 RNA by the double-stranded RNA deaminase ADAR1 stimulates viral infection. Nucleic Acids Res. 2009;37(17):5848–58.
109. Anne Cachat SA, Sébastien A, Chevalier C, Journo F, Fusil. Hélène Dutartre, Adrien Boniface1, Nga Ling Ko, Antoine Gessain, François-Loïc Cosset, Rodolphe Suspène, Jean-Pierre Vartanian, Renaud Mahieux. ADAR1 enhances HTLV-1 and HTLV-2 replication through inhibition of PKR activity. Retrovirology. 2014;11:93.
110. Ko NL, Birlouez E, Wain-Hobson S, Mahieux R, Vartanian JP. Hyperediting of human T-cell leukemia virus type 2 and simian T-cell leukemia virus type 3 by the dsRNA adenosine deaminase ADAR-1. J Gen Virol. 2012;93(Pt 12):2646–51.
111. Taura M, Song E, Ho YC, Iwasaki A. Apobec3A maintains HIV-1 latency through recruitment of epigenetic silencing machinery to the long terminal repeat. Proc Natl Acad Sci U S A. 2019;116(6):2282–9.
112. Holmes RK, Koning FA, Bishop KN, Malim MH. APOBEC3F can inhibit the accumulation of HIV-1 reverse transcription products in the absence of hypermutation. Comparisons with APOBEC3G. J Biol Chem. 2007;282(4):2587–95.
113. Yoshikawa R, Izumi T, Nakano Y, Yamada E, Moriwaki M, Misawa N, et al. Small ruminant lentiviral vif proteins commonly utilize cyclophilin A, an evolutionarily and structurally conserved protein, to degrade ovine and caprine APOBEC3 proteins. Microbiol Immunol. 2016;60(6):427–36.
114. Yoshikawa R, Takeuchi JS, Yamada E, Nakano Y, Misawa N, Kimura Y, et al. Feline immunodeficiency Virus evolutionarily acquires two proteins, vif and protease, capable of antagonizing Feline APOBEC3. J Virol. 2017;91(11):e00250–17.
115. Pan T, He X, Chen B, Chen H, Geng G, Luo H, et al. Development of benzimidazole derivatives to inhibit HIV-1 replication through protecting APOBEC3G protein. Eur J Med Chem. 2015;95:500–13.
116. Gourraud PA, Karaouni A, Woo JM, Schmidt T, Oksenberg JR, Hecht FM, et al. APOBEC3H haplotypes and HIV-1 pro-viral vif DNA sequence diversity in early untreated human immunodeficiency virus-1 infection. Hum Immunol. 2011;72(3):207–12.
117. Britan-Rosich E, Nowarski R, Kotler M. Multifaceted counter-APOBEC3G mechanisms employed by HIV-1 Vif. J Mol Biol. 2011;410(5):1065–76.
118. MacMillan AL, Kohli RM, Ross SR. APOBEC3 inhibition of mouse mammary tumor virus infection: the role of cytidine deamination versus inhibition of reverse transcription. J Virol. 2013;87(9):4808–17.
119. Stavrou S, Nitta T, Kotla S, Ha D, Nagashima K, Rein AR, et al. Murine leukemia virus glycosylated gag blocks apolipoprotein B editing complex 3 and cytosolic sensor access to the reverse transcription complex. Proc Natl Acad Sci U S A. 2013;110(22):9078–83.
120. Clerzius G, Gelinas JF, Daher A, Bonnet M, Meurs EF, Gatignol A. ADAR1 interacts with PKR during human immunodeficiency virus infection of lymphocytes and contributes to viral replication. J Virol. 2009;83(19):10119–28.
121. Vieira VC, Soares MA. The role of cytidine deaminases on innate immune responses against human viral infections. Biomed Res Int. 2013;2013:683095.
122. McDonnell MM, Karvonen SC, Gaba A, Flath B, Chelico L, Emerman M. Highly-potent, synthetic APOBEC3s restrict HIV-1 through deamination-independent mechanisms. PLoS Pathog. 2021;17(6):e1009523.
123. Schafer A, Bogerd HP, Cullen BR. Specific packaging of APOBEC3G into HIV-1 virions is mediated by the nucleocapsid domain of the gag polyprotein precursor. Virology. 2004;328(2):163–8.
124. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220(4599):868–71.
125. Wang X, Ao Z, Chen L, Kobinger G, Peng J, Yao X. The cellular antiviral protein APOBEC3G interacts with HIV-1 reverse transcriptase and inhibits its function during viral replication. J Virol. 2012;86(7):3777–86.
126. Verhalen B, Starrett GJ, Harris RS, Jiang M. Functional upregulation of the DNA cytosine deaminase APOBEC3B by Polyomaviruses. J Virol. 2016;90(14):6379–86.
127. Cheng AZ, Yockteng-Melgar J, Jarvis MC, Malik-Soni N, Borozan I, Carpenter MA, et al. Epstein-Barr virus BORF2 inhibits cellular APOBEC3B to preserve viral genome integrity. Nat Microbiol. 2019;4(1):78–88.
128. Yang Y, Wang H, Zhang X, Huo W, Qi R, Gao Y, et al. Heat increases the editing efficiency of human papillomavirus E2 gene by inducing upregulation of APOBEC3A and 3G. J Invest Dermatol. 2017;137(4):810–8.
129. Pautasso S, Galitska G, Dell'Oste V, Biolatti M, Cagliani R, Forni D, et al. Strategy of human cytomegalovirus to escape Interferon Beta-Induced APOBEC3G editing activity. J Virol. 2018;92(19):e01224–18.
130. Gee P, Ando Y, Kitayama H, Yamamoto SP, Kanemura Y, Ebina H, et al. APOBEC1-mediated editing and attenuation of herpes simplex virus 1 DNA indicate that neurons have an antiviral role during herpes simplex encephalitis. J Virol. 2011;85(19):9726–36.
131. Wang Y, Li X, Song S, Sun Y, Zhang J, Yu C, et al. HPV11 E6 mutation by overexpression of APOBEC3A and effects of interferon-omega on APOBEC3s and HPV11 E6 expression in HPV11.HaCaT cells. Virol J. 2017;14(1):211.
132. Ma Z, Ni G, Damania B. Innate sensing of DNA virus genomes. Annu Rev Virol. 2018;5(1):341–62.
133. Yuan L, Jia Q, Yang S, Idris NFB, Li Y, Wang Y, et al. ADAR1 promotes HBV replication through its deaminase domain. Front Biosci (Landmark Ed). 2020;25(4):710–21.
134. Kao JH, Chen DS. Global control of hepatitis B virus infection. Lancet Infect Dis. 2002;2(7):395–403.
135. Meng Z, Chen Y, Lu M. Advances in targeting the innate and adaptive immune systems to cure chronic hepatitis B virus infection. Front Immunol. 2019;10:3127.
136. Chen Y, Hu J, Cai X, Huang Y, Zhou X, Tu Z, et al. APOBEC3B edits HBV DNA and inhibits HBV replication during reverse transcription. Antiviral Res. 2018;149:16–25.
137. Zhang W, Zhang X, Tian C, Wang T, Sarkis PT, Fang Y, et al. Cytidine deaminase APOBEC3B interacts with heterogeneous nuclear ribonucleoprotein K and suppresses hepatitis B virus expression. Cell Microbiol. 2008;10(1):112–21.
138. Chen Y, Shen B, Zheng X, Long Q, Xia J, Huang Y, et al. DHX9 interacts with APOBEC3B and attenuates the anti-HBV effect of APOBEC3B. Emerg Microbes Infect. 2020;9(1):366–77.
139. Baumert TF, Rosler C, Malim MH, von Weizsacker F. Hepatitis B virus DNA is subject to extensive editing by the human deaminase APOBEC3C. Hepatology. 2007;46(3):682–9.
140. Kock J, Blum HE. Hypermutation of hepatitis B virus genomes by APOBEC3G, APOBEC3C and APOBEC3H. J Gen Virol. 2008;89(Pt 5):1184–91.
141. Bonvin M, Achermann F, Greeve I, Stroka D, Keogh A, Inderbitzin D, et al. Interferon-inducible expression of APOBEC3 editing enzymes in human

hepatocytes and inhibition of hepatitis B virus replication. Hepatology. 2006;43(6):1364–74.
142. Lei YC, Tian YJ, Ding HH, Wang BJ, Yang Y, Hao YH, et al. N-terminal and C-terminal cytosine deaminase domain of APOBEC3G inhibit hepatitis B virus replication. World J Gastroenterol. 2006;12(46):7488–96.
143. Nair S, Zlotnick A. Asymmetric modification of Hepatitis B Virus (HBV) genomes by an endogenous cytidine deaminase inside HBV Cores informs a model of reverse transcription. J Virol. 2018;92(10):e02190–17.
144. Suspene R, Guetard D, Henry M, Sommer P, Wain-Hobson S, Vartanian JP. Extensive editing of both hepatitis B virus DNA strands by APOBEC3 cytidine deaminases in vitro and in vivo. Proc Natl Acad Sci U S A. 2005;102(23):8321–6.
145. Nguyen DH, Gummuluru S, Hu J. Deamination-independent inhibition of hepatitis B virus reverse transcription by APOBEC3G. J Virol. 2007;81(9):4465–72.
146. Noguchi C, Hiraga N, Mori N, Tsuge M, Imamura M, Takahashi S, et al. Dual effect of APOBEC3G on Hepatitis B virus. J Gen Virol. 2007;88(Pt 2):432–40.
147. Liddicoat BJ, Piskol R, Chalk AM, Ramaswami G, Higuchi M, Hartner JC, et al. RNA editing by ADAR1 prevents MDA5 sensing of endogenous dsRNA as nonself. Science. 2015;349(6252):1115–20.
148. Li Q, Gloudemans MJ, Geisinger JM, Fan B, Aguet F, Sun T, et al. RNA editing underlies genetic risk of common inflammatory diseases. Nature. 2022;608(7923):569–77.
149. Gabay O, Shoshan Y, Kopel E, Ben-Zvi U, Mann TD, Bressler N, et al. Landscape of adenosine-to-inosine RNA recoding across human tissues. Nat Commun. 2022;13(1):1184.

Publisher's note