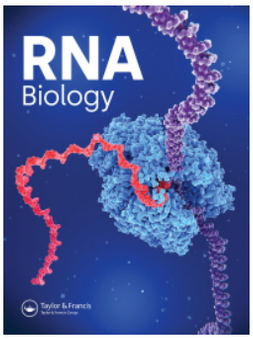

RNA Biology

ISSN: 1547-6286 (Print) 1555-8584 (Online) Journal homepage: www.tandfonline.com/journals/krnb20

An elusive debate on the evidence for RNA editing in SARS-CoV-2

Giorgio Mattiuz, Salvatore Di Giorgio & Silvestro G. Conticello

To cite this article: Giorgio Mattiuz, Salvatore Di Giorgio & Silvestro G. Conticello (2024) An elusive debate on the evidence for RNA editing in SARS-CoV-2, RNA Biology, 21:1, 371-372, DOI: 10.1080/15476286.2024.2321032

To link to this article: https://doi.org/10.1080/15476286.2024.2321032

Published online: 01 Mar 2024.

RNA BIOLOGY
2024, VOL. 21, NO. 1, 371–372
https://doi.org/10.1080/15476286.2024.2321032

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

An elusive debate on the evidence for RNA editing in SARS-CoV-2

Giorgio Mattiuz [a], Salvatore Di Giorgio [b], and Silvestro G. Conticello [c,d]

[a]Department of Experimental and Clinical Medicine, University of Florence, Firenze, Italy; [b]German Cancer Research Center (DKFZ) - Division of Immune Diversity, Foundation under Public Law, Heidelberg, Germany; [c]Core Research Laboratory, ISPRO, Firenze, Italy; [d]Institute of Clinical Physiology, National Research Council, Pisa, Italy

ARTICLE HISTORY Revised 12 February 2024; Accepted 14 February 2024

Dear Editor,

In a recent review [1] Pu and Colleagues discuss a supposedly ongoing debate on the source of mutations in the SARS-CoV-2 virus: many have reported a bias in intra- and inter-host viral mutations, leading to the hypothesis that host deaminases act on the virus [e.g [2–25], and a few noted that – especially for A>G changes – specific pipelines should be used to avoid overestimates [7,26,27].

Our hypothesis stemmed from the striking difference between SARS-CoV replication errors shown in Smith et al. [28] (with an enrichment in transversions over transitions, and T>G being the main nucleotide change) and the profile we, and others, have observed. The lack of enrichment for C>U and A>G misincorporation by the viral replication complex has been, indeed, confirmed recently in vitro [29].

The Authors of the review criticize our original analysis [2] based on the poor separation between 'editing' signal from other mutational signals, and on the symmetry of the mutational profiles (C>T levels similar to G>A ones; A>G levels similar to T>C ones). The Authors suggest that this presumed flaw points to either replication or sequencing errors. While we agree that intra-host datasets may be biased by sequencing errors, a similar profile is observed also in inter-host datasets (which derive from consensus sequences, typically unaffected by background noise due to sequencing errors).

The authors support their suggestion on the basis of having redrawn in Fig. 1A our own data. In fact, the graph in this figure looks quite different from our own presentation of the data, both when intra-host or inter-host data are considered [2]. We have tried to obtain their figure using our data, but despite our efforts we have been unable to obtain the pattern (Fig. 1A) that is central to their argument. We thus stand by our original hypothesis and, for a longer discussion on the 'debate', we refer to a past commentary [30].

In the end, it might be useful to remember that final evidence for the role of the host deaminases in the evolution of the SARS-CoV-2 will only be experimental. While nothing is available yet for the ADARs, initial experimental evidence on the role of the APOBECs is already available [31,32], which seems to have escaped the Authors' attention.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Giorgio Mattiuz http://orcid.org/0000-0002-9668-1706
Salvatore Di Giorgio http://orcid.org/0000-0002-1419-717X
Silvestro G. Conticello http://orcid.org/0000-0002-4244-1846

References

[1] Pu X, Xu Q, Wang J, et al. The continuing discovery on the evidence for RNA editing in SARS-CoV-2. RNA Biol. 2023;20(1):219–222. doi: 10.1080/15476286.2023.2214437
[2] Di Giorgio S, Martignano F, Torcia MG, et al. Evidence for host-dependent RNA editing in the transcriptome of SARS-CoV-2. Sci Adv. 2020;6(25). doi: 10.1126/sciadv.abb5813
[3] Graudenzi A, Maspero D, Angaroni F, et al. Mutational signatures and heterogeneous host response revealed via large-scale characterization of SARS-CoV-2 genomic diversity. iScience. 2021;24(2):102116. doi: 10.1016/j.isci.2021.102116
[4] Gregori J, Cortese MF, Piñana M, et al. Host-dependent editing of SARS-CoV-2 in COVID-19 patients. Emerg Microbes Infect. 2021;10(1):1777–1789. doi: 10.1080/22221751.2021.1969868
[5] Lythgoe KA, Hall M, Ferretti L, et al. SARS-CoV-2 within-host diversity and transmission. Science. 2021;372(6539). doi: 10.1126/science.abg0821
[6] Pathak AK, Mishra GP, Uppili B, et al. Spatio-temporal dynamics of intra-host variability in SARS-CoV-2 genomes. Nucleic Acids Res. 2022;50(3):1551–1561. doi: 10.1093/nar/gkab1297
[7] Picardi E, Mansi L, Pesole G. Detection of A-to-I RNA editing in SARS-COV-2. Genes. 2021;13(1):41 doi: 10.3390/genes13010041
[8] Popa A, Genger J-W, Nicholson MD, et al. Genomic epidemiology of superspreading events in Austria reveals mutational dynamics and transmission properties of SARS-CoV-2. Sci Transl Med. 2020;12(573). doi: 10.1126/scitranslmed.abe2555
[9] Song Y, He X, Yang W, 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):2509–2521. doi: 10.1093/nar/gkac120

CONTACT Silvestro G. Conticello silvestro.conticello@cnr.it Institute of Clinical Physiology, National Research Council, Pisa 56124, Italy

[10] Tonkin-Hill G, Martincorena I, Amato R, et al. Patterns of within-host genetic diversity in SARS-CoV-2. Elife. 2021. doi: 10.7554/eLife.66857
[11] Voloch CM, da Silva FR Jr, De Almeida LGP, et al. Intra-host evolution during SARS-CoV-2 prolonged infection. Virus Evol. 2021;7(2). doi: 10.1093/ve/veab078
[12] Wang Y, Wang D, Zhang L, et al. Intra-host variation and evolutionary dynamics of SARS-CoV-2 populations in COVID-19 patients. Genome Med. 2021;13(1):
[13] Azgari C, Kilinc Z, Turhan B, et al. The mutation profile of SARS-CoV-2 is primarily shaped by the Host antiviral defense. Viruses. 2021;10(3):394.
[14] Deng S, Xing K, He X Mutation signatures inform the natural host of SARS-CoV-2. bioRxiv 2021. doi: 10.1101/2021.07.05.451089
[15] Friedman N, Jacob-Hirsch J, Drori Y, et al. Transcriptomic profiling and genomic mutational analysis of human coronavirus (HCoV)-229E -infected human cells. PloS One. 2021;16(2):e0247128. doi: 10.1371/journal.pone.0247128
[16] Klimczak LJ, Randall TA, Saini N, et al. Similarity between mutation spectra in hypermutated genomes of rubella virus and in SARS-CoV-2 genomes accumulated during the COVID-19 pandemic. PloS One. 2020;15(10):e0237689. doi: 10.1371/journal.pone.0237689
[17] Kosuge M, Furusawa-Nishii E, Ito K, et al. Point mutation bias in SARS-CoV-2 variants results in increased ability to stimulate inflammatory responses. Sci Rep. 2020;10(1):17766. doi: 10.1038/s41598-020-74843-x
[18] Matyášek R, Řehůřková K, Berta Marošiová K, et al. Mutational asymmetries in the SARS-CoV-2 genome May Lead to increased hydrophobicity of virus proteins. Genes. 2021;10(6):826. doi: 10.3390/genes12060826
[19] Pang X, Li P, Zhang L, et al. Emerging severe acute respiratory syndrome coronavirus 2 mutation hotspots associated with clinical outcomes and transmission. Front Microbiol. 2021. doi: 10.3389/fmicb.2021.753823.
[20] Rice AM, Castillo Morales A, Ho AT, et al. Evidence for Strong Mutation Bias toward, and selection against, U content in SARS-CoV-2: implications for vaccine design. Mol Biol Evol. 2021. doi: 10.1093/molbev/msaa188
[21] Sadykov M, Mourier T, Guan Q, et al. Short sequence motif dynamics in the SARS-CoV-2 genome suggest a role for cytosine deamination in CpG reduction. J Mol Cell Biol. 2021;13(3):225–227. doi: 10.1093/jmcb/mjab011
[22] Simmonds P, Schwemmle M. 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). doi: 10.1128/mSphere.00408-20
[23] Simmonds P, Ansari MA, Pichlmair A. 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. doi: 10.1371/journal.ppat.1009596
[24] Tasakis RN, Samaras G, Jamison A, et al. SARS-CoV-2 variant evolution in the United States: high accumulation of viral mutations over time likely through serial Founder events and mutational bursts. PloS One. 2021;16(7):e0255169. doi: 10.1371/journal.pone.0255169
[25] Van Dorp L, Richard D, Tan CCS, et al. No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2. Nat Commun. 2020;11(1):5986. doi: 10.1038/s41467-020-19818-2
[26] Cai H, Liu X, Zheng X. RNA editing detection in SARS-CoV-2 transcriptome should be different from traditional SNV identification. J Appl Genet. 2022;63(3):587–594. doi: 10.1007/s13353-022-00706-y
[27] Song Y, He X, Yang W, 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):2509–2521. doi: 10.1093/nar/gkac120
[28] Smith EC, Blanc H, Vignuzzi M, et al. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. PloS Pathog. 2013;9(8):e1003565. doi: 10.1371/journal.ppat.1003565
[29] Yin X, Popa H, Stapon A, et al. Fidelity of ribonucleotide incorporation by the SARS-CoV-2 replication complex. J Mol Biol. 2023;435(5):167973. doi: 10.1016/j.jmb.2023.167973
[30] Martignano F, Di Giorgio S, Mattiuz G, et al. Commentary on "poor evidence for host-dependent regular RNA editing in the transcriptome of SARS-CoV-2". J Appl Genet. 2022;63(2).
[31] Kim K, Calabrese P, Wang S, et al. The roles of APOBEC-mediated RNA editing in SARS-CoV-2 mutations, replication and fitness. Sci Rep. 2022;12(1):14972. doi: 10.1038/s41598-022-19067-x
[32] Nakata Y, Ode H, Kubota M, et al. Cellular APOBEC3A deaminase drives mutations in the SARS-CoV-2 genome. Nucleic Acids Res. 2023;51(2):783–795. doi: 10.1093/nar/gkac1238