ORF8/ORF8a: a difference between SARS-CoV-2 and SARS-CoV

Received: 29 Oct 2021
Accepted: 29 Nov 2021

To the Editor:

Recently in an editorial published as an "early view" paper in the *European Respiratory Journal*, Hartsell *et al*. [1] reported that ORF8a has a role in SARS-CoV-2 infection. In figure 1, it was stated that ORF7a, ORF8a and ORF9b locate within the mitochondria and can inhibit RIG1-MAVS (retinoic acid-inducible gene I-mitochondrial antiviral signalling protein)-dependent interferon signalling, enhance viral replication and disrupt mitochondrial function [1], although based on scientific evidence, SARS-CoV-2 lacks ORF8a [2–4].

The genome of SARS-CoV-2 contains several accessory genes in the 3′-end of the genome that code nine accessory proteins (3a, 3b, 6, 7a, 7b, 8, 9b, 9c and 10), which are involved in SARS-CoV-2 infection (figure 1) [5]. SARS-CoV-2 ORF8 is a 121-amino acid protein which contains an N-terminal signal sequence which is followed by a predicted Ig-like fold. ORF8 protein has a signal sequence for import into the endoplasmic reticulum to interact with proteins of the host cell [6]. ORF8a is absent in SARS-CoV-2 because of a 29-nucleotide deletion that inactivates the formation of the ORF8ab tandem. ORF8 is split into two separated ORFs (ORF8a and ORF8b) in SARS-CoV.

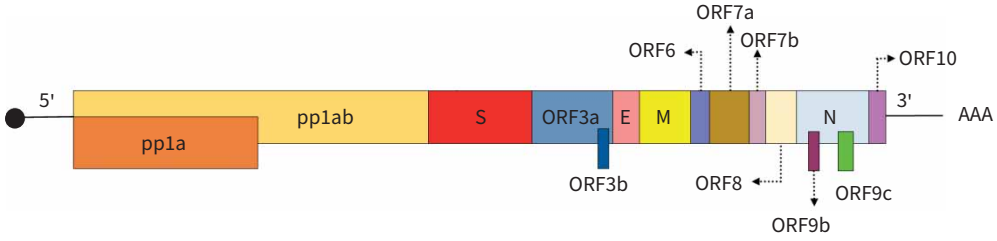

FIGURE 1 SARS-CoV-2 genome.

An intact ORF8 is encoded by SARS-CoV-2 that shares the least homology among SARS-CoV-2 and SARS-CoV proteins [7]. SARS-CoV-2 encodes two viral proteins with ion channel activity (viroporin): 3a and E [8], but SARS-CoV encodes three: proteins 3a, E and 8a [9]. In SARS-CoV, ORF8 gene encodes two proteins, ORF8a and ORF8b, which characterise proteins of 39 and 84 amino acids, respectively [10]. ORF8a can induce apoptosis by a mitochondrion-dependent pathway [11].

In SARS-CoV-2, ORF8 has several functions during infection. ORF8 can disrupt IFN-I signalling when exogenously overexpressed in cells; it also downregulates levels of major histocompatibility complex (MHC) class I through direct binding [6], however this process is not observed for ORF8a and ORF8b. Furthermore, ORF8 degrades MHC-I *via* the autophagy pathway.

In conclusion, one of the differences between SARS-CoV-2 and SARS-CoV is ORF8/ORF8a, for which the SARS-CoV-2 genome encodes an intact ORF8; however, SARS-CoV encodes two proteins, ORF8a and ORF8b.

Shareable abstract (@ERSpublications)
ORF8 as an accessory protein of SARS-CoV-2 https://bit.ly/3Gr3OTK

Cite this article as: Zandi M. ORF8/ORF8a: a difference between SARS-CoV-2 and SARS-CoV. *Eur Respir J* 2022; 59: 2102818 [DOI: 10.1183/13993003.02818-2021].

Milad Zandi [1,2]

[1]Dept of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. [2]Research Center for Clinical Virology, Tehran University of Medical Sciences, Tehran, Iran.

Corresponding author: Milad Zandi (Miladzandi416@gmail.com)

The points raised in this letter relate to the early view version of the editorial by E.M. Hartsell and co-workers. The editorial is published in its final form in this issue of the *European Respiratory Journal*, and has been amended by the authors to remove any factual errors. The correction is noted in the final version of the editorial: https:/doi.org/10.1183/13993003.02417-2021

Conflict of interest: M. Zandi declares no conflict of interest for this article.

References

1 Hartsell EM, Gillespie MN, Langley RJ. Does acute and persistent metabolic dysregulation in COVID-19 point to novel biomarkers and future therapeutic strategies? *Eur Respir J* 2022; 59: 2102417.
2 Farrag MA, Amer HM, Bhat R, *et al.* SARS-CoV-2: an overview of virus genetics, transmission, and immunopathogenesis. *Int J Environ Res Public Health* 2021; 18: 6312.
3 V'kovski P, Kratzel A, Steiner S, *et al.* Coronavirus biology and replication: implications for SARS-CoV-2. *Nat Rev Microbiol* 2021; 19: 155–170.
4 Zhang Y, Chen Y, Li Y, *et al.* The ORF8 protein of SARS-CoV-2 mediates immune evasion through down-regulating MHC-I. *Proc Natl Acad Sci USA* 2021; 118: e2024202118.
5 Kesheh MM, Hosseini P, Soltani S, *et al.* An overview on the seven pathogenic human coronaviruses. *Rev Med Virol* 2021; in press [https://doi.org/10.1002/rmv.2282].
6 Flower TG, Buffalo CZ, Hooy RM, *et al.* Structure of SARS-CoV-2 ORF8, a rapidly evolving immune evasion protein. *Proc Natl Acad Sci USA* 2021; 118: e2021785118.
7 Zandi M. ORF8a as a viroporin in SARS-CoV-2 infection? *Cytokine Growth Factor Rev* 2021; 61: 1.
8 Kern DM, Sorum B, Mali SS, *et al.* Cryo-EM structure of SARS-CoV-2 ORF3a in lipid nanodiscs. *Nat Struct Mol Biol* 2021; 28: 573–582.
9 Castaño-Rodriguez C, Honrubia JM, Gutiérrez-Álvarez J, *et al.* Role of severe acute respiratory syndrome coronavirus viroporins E, 3a, and 8a in replication and pathogenesis. *MBio* 2018; 9: e02325-17.
10 Mohammad S, Bouchama A, Mohammad Alharbi B, *et al.* SARS-CoV-2 ORF8 and SARS-CoV ORF8ab: genomic divergence and functional convergence. *Pathogens* 2020; 9: 677.
11 Chen C-Y, Ping Y-H, Lee H-C, *et al.* Open reading frame 8a of the human severe acute respiratory syndrome coronavirus not only promotes viral replication but also induces apoptosis. *J Infect Dis* 2007; 196: 405–415.