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

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.

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.
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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

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References

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