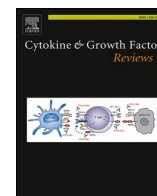




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## ORF8a as a viroporin in SARS-CoV-2 infection?

The seventh human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is described as the causative agent of coronavirus infectious disease (COVID-19) [1]. Since the first detection of SARS-CoV-2 in late December 2019 [2], the virus and ongoing COVID-19 pandemic have spread across the globe, killing more than 4 million individuals in the past 18 months. Highly efficacious vaccines generated by biotech and pharma remain the only solution to this international crisis.

The SARS-CoV-2 harbors a positive-sense single-stranded RNA in order of 5'-replicase (ORF1a/b)-S-E-M-N-poly(A)-3', also the SARS-CoV-2 genome contains several ORFs at its 3' portion which encodes accessory proteins including ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c as well as ORF10 [3,4]. The scientific evidence shows that the genome of SARS-CoV-2 lacks ORF8a [5–8].

Indeed, both ORF8a and ORF8b are absent in SARS-CoV-2 because of a 29-nucleotide deletion that inactivates the formation ORF8ab tandem [9], while ORF8a and ORF8b are present in SARS-CoV [5,10]. In SARS-CoV, ORF8 splitting into two separated ORFs (ORF8a and ORF8b) [11]. In addition, ORF3b of SARS-CoV is longer than its ortholog in SARS-CoV-2 [8,12].

The SARS-CoV-2 encodes an intact ORF8, which among all the viral proteins of SARS-CoV-2 and SARS-CoV shares the least homology [13]. The ORF8 protein, one of the accessory proteins of SARS-CoV-2, can downregulate surface and total levels of MHC-1 by direct binding and can also degrade MHC-1 by the autophagy pathway [13]. In addition, the ORF8 protein prevents antigen presentation system and CTL-mediated killing of cells that infected with SARS-CoV-2 [14,15].

I have recently read with interest an article by Ni Zhao et al. the authors reported that SARS-CoV-2 can encode a set of accessory proteins, including two ion-channel proteins known as viroporins (open reading frame 3a (ORF3a) and ORF8a) [16], while according to scientific evidence, SARS-CoV-2 lacks ORF8a, and this protein (ORF8a) has no role in SARS-CoV-2 infection.

### Declaration of Competing Interest

The author reports no declarations of interest.

### References

- [1] S.K. Mohanty, et al., Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19)—anatomic pathology perspective on current knowledge, *Diagn. Pathol.* 15 (1) (2020) 1–17.
- [2] A.H. Navand, et al., Diabetes and coronavirus infections (SARS-CoV, MERS-CoV, and SARS-CoV-2), *J. Acute Dis.* 9 (6) (2020) 244.
- [3] A. Mohammad, et al., Molecular simulation-based investigation of highly potent natural products to abrogate formation of the nsp10–nsp16 complex of sars-cov-2, *Biomolecules* 11 (4) (2021) 573.
- [4] J. Zhang, et al., A systemic and molecular study of subcellular localization of SARS-CoV-2 proteins, *Signal Transduct. Target. Ther.* 5 (1) (2020) 1–3.
- [5] G. Mariano, et al., Structural characterization of SARS-CoV-2: where we are, and where we need to be, *Front. Mol. Biosci.* 7 (2020) 344.
- [6] M.A. Farrag, et al., SARS-CoV-2: an overview of virus genetics, transmission, and immunopathogenesis, *Int. J. Environ. Res. Public Health* 18 (12) (2021) 6312.
- [7] H. Geng, et al., SARS-CoV-2 ORF8 forms intracellular aggregates and inhibits IFN $\gamma$ -induced antiviral gene expression in human lung epithelial cells, *Front. Immunol.* 12 (2021) 2108.
- [8] P. V'kovski, et al., Coronavirus biology and replication: implications for SARS-CoV-2, *Nat. Rev. Microbiol.* 19 (3) (2021) 155–170.
- [9] R.Y. Neches, N.C. Kyripides, C.A. Ouzounis, Atypical divergence of SARS-CoV-2 Orf8 from Orf7a within the coronavirus lineage suggests potential stealthy viral strategies in immune evasion, *Mbio* 12 (1) (2021) e03014–20.
- [10] T.M. Nguyen, Y. Zhang, P.P. Pandolfi, Virus against Virus: a Potential Treatment for 2019-nCoV (SARS-CoV-2) and Other RNA Viruses, Nature Publishing Group, 2020.
- [11] G. Mariano, et al., Structural characterization of SARS-CoV-2: where we are, and where we need to be, *Front. Mol. Biosci.* 7 (2020).
- [12] M. Sa Ribero, et al., Interplay between SARS-CoV-2 and the type 1 interferon response, *PLoS Pathog.* 16 (7) (2020) e1008737.
- [13] Y. Zhang, et al., The ORF8 protein of SARS-CoV-2 mediates immune evasion through down-regulating MHC-I, *Proc. Natl. Acad. Sci. U. S. A.* 118 (23) (2021).
- [14] M.D. Park, Immune evasion via SARS-CoV-2 ORF8 protein? *Nat. Rev. Immunol.* 20 (7) (2020) 408.
- [15] Y. Zhang, et al., The ORF8 protein of SARS-CoV-2 mediates immune evasion through down-regulating MHC-I, *Proc. Natl. Acad. Sci. U. S. A.* 118 (23) (2021).
- [16] N. Zhao, B. Di, L.-l. Xu, The NLRP3 inflammasome and COVID-19: activation, pathogenesis and therapeutic strategies, *Cytokine Growth Factor Rev.* (2021).



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