ORF9c and ORF10 as accessory proteins of SARS-CoV-2 in immune evasion

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In a recent Perspective article in *Nature Reviews Immunology* (Wong, L-Y. R. & Perlman, S. Immune dysregulation and immunopathology induced by SARS-CoV-2 and related coronaviruses — are we our own worst enemy? *Nat. Rev. Immunol.* **22**, 47–56 (2022))[1], Lok-Yin Roy Wong and Stanley Perlman described how the SARS-CoV-2 genome encodes seven accessory proteins that may contribute to immune evasion: ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8 and ORF9b. However, there is evidence that the genome of SARS-CoV-2 encodes more than seven accessory proteins. The authors did not mention ORF9c and ORF10, both of which have been suggested to have roles in the immune evasion process[2,3].

The overexpression of ORF10 significantly inhibited the expression of type I interferon genes and interferon-stimulated genes by SARS-CoV-2-infected HeLa cells in vitro[3]. ORF10 was shown to inhibit the interferon signalling pathway by binding to mitochondrial antiviral signalling protein (MAVS)[3], thus, MAVS may be degraded via the ORF10-induced autophagy pathway. In addition, overexpression of ORF10 was reported to induce the mitophagy process by increasing the accumulation of LC3 in mitochondria[3,4]. A preprint article by Andres et al. reported that the ORF9c accessory protein of SARS-CoV-2 interferes with antigen presentation, interferon signalling, and other immune and stress pathways in the human lung epithelial cell line A549, suggesting that it may also be involved in the immune evasion process[2]. Important caveats here are that these experiments were performed using in vitro overexpression systems, and it is still unclear whether these proteins are expressed in virally infected cells in the context of an in vivo SARS-CoV-2 infection. Furthermore, ORF10 may be variably expressed by different isolates of SARS-CoV-2.

In summary, as well as the seven accessory proteins detailed in the Perspective by Wong and Perlman, the SARS-CoV-2 genome may encode two additional accessory proteins, ORF9c and ORF10, that can play key roles in the viral replication and immune evasion processes. However, further study is necessary to clarify the roles of ORF9c and ORF10 in the context of in vivo infections with SARS-CoV-2.

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Competing interests
The author declares no competing interests.