Effect of SARS-CoV-2 ORF3C on human lung cells metabolism

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Abstract:
SARS-CoV-2 encodes, in addition to structural and non-structural proteins, a variable number of accessory proteins that can contribute to host adaptation, modulation of immune responses and virulence. However, although they could be a promising target for antivirals, the molecular functions of many accessory proteins remain largely unknown due to the lack of homology with other known proteins.
In this work, we focused on the study of the ORF3c,a protein of 40-41 amino acids, with a molecular mass of 4.9 kDa and a pI of 10.9.
In particular , we have investigated human and bat ORF3c effect on the metabolism of HSAEC1 healthy human lung cells.
Cells transiently transfected with human or bat ORF3c showed a higher mitochondrial respiration and a decrease in basal glycolysis compared to cells transfected with the empty plasmid as a control; moreover also mitochondrial fatty acids oxidation was higher in the presence of both ORF3c respect to control.
The amount of reactive oxygen species was also investigated: a decrease in the production of generic ROS at the cytoplasmic level was observed in cells transfected with bat ORF3c, accompanied by a high production of superoxide anion and a lower SOD1 enzymatic activity. In contrast, cells expressing human ORF3c showed an enhanced production of hydrogen peroxide at the mitochondrial level. At the same time, the specific activities of GST, GR and GPox showed a slight increase in cells expressing both ORF3c.
The amount of transcript of HMOX1, an antioxidant and marker of ferroptosis, was also evaluated and found to be significantly overexpressed in both conditions. Considering that HMOX1 is activated by elevated free iron in cytosol, ORF3c could lead to ferroptosis.
These metabolic rearrangements, that mimic what happens during the fatal phase of SARS-CoV-2 infection, lead us to hypothesize that ORF3c has a key role in this phase and could provide a new target for vaccine or antiviral strategies.