

THE HUMAN PROTEIN ATLAS

New findings on enzymes with an important role for SARS-CoV-2 infection

Researchers within the Human Protein Atlas have described the presence of the enzyme ACE2 in the entire human body, which is suggested to be the key protein used by the SARS-CoV-2 virus for host cell entry and development of the disease COVID-19. In contrast to previous studies, the study shows that none or only very low levels of ACE2 protein is present in the normal respiratory system. The results are presented in *Molecular Systems Biology*.

The article presents a large-scale systematic evaluation of Angiotensin I converting enzyme 2 (ACE2) expression in more than 150 different cell types both on the mRNA and protein level, and reports that ACE2 is expressed at very low levels – if any – in respiratory epithelial cells.

“Considering the clinical manifestation of COVID-19 with acute respiratory distress syndrome and extensive damage to the lung parenchyma, the results highlight the need to further study the biological mechanisms responsible for infection and disease progression in COVID-19 disease”, says Dr. Cecilia Lindskog, senior author on the paper and Head Director of the Human Protein Atlas tissue team at Uppsala University.

For a full understanding of the susceptibility for SARS-CoV-2 infection and the progression to severe and fatal disease, it is necessary to study the SARS-CoV-2 entry receptors and their cell type-specific expression in human tissues, both on the mRNA and protein level. It has been suggested that SARS-CoV-2 employs the enzyme ACE2 for host cell entry, and that entry of SARS-CoV-2 via this receptor would explain the severe clinical manifestations observed in various tissues and organs, including the respiratory system.

The study by Hikmet *et al* presents a comprehensive update on ACE2 expression across the entire human body, both on the mRNA and protein levels. High expression was consistently observed in the intestines, kidney, gallbladder, heart, male reproductive organs, placenta, eye, and vascular system. In the respiratory system, the expression was however limited, with no or only low expression in a subset of cells in a few individuals.

“Previous studies have suggested that ACE2 protein is highly expressed in human lung, but these expression profiles have not been reliably presented alongside with tissues and organs from the entire human body, or based on several different datasets on the mRNA and protein level”, says Dr. Cecilia Lindskog. “We could here confidently show that none or only very low levels of ACE2 protein is present in the normal respiratory system, which is in contrast to previous studies.”

The immunohistochemical analysis was based on the Human Protein Atlas (HPA) resource and an extended patient cohort of 360 different normal lung samples, using two different antibodies that were stringently validated.

“The HPA program has spent a considerable effort on introducing and implementing a new concept for enhanced validation of antibodies using strategies proposed by the International Working Group for Antibody Validation (IWGAV). Such strategies are crucial for determining if the antibody staining corresponds to true protein expression”, says Prof. Mathias Uhlén, Director of the HPA consortium and co-author on the paper.

In a News & Views article published alongside with the ACE2 paper, Nawijn *et al* acknowledge the importance of the study and discuss potential explanations for the low expression in the respiratory system. Recent studies suggest that ACE2 could be an interferon-induced gene, leading to upregulation during SARS-CoV-2 infection. It is proposed that ACE2 may first enter and infect eye conjunctiva and cells in the upper airways, followed by upregulation of ACE2 due to the antiviral response, which allows the SARS-CoV-2 to spread and infect the lung parenchyma. It has also been suggested that smoking may increase the ACE2 expression in the respiratory system.

“Further studies are urgently needed to study the dynamic regulation of ACE2, and to confirm whether the low ACE2 expression in the human respiratory system is sufficient for SARS-CoV-2 infection, or if other factors are needed for host cell entry”, says Cecilia Lindskog.

Read the full article on ACE2:

Hikmet et al <https://www.embopress.org/doi/10.15252/msb.20209610>

Read the News & Views article on the same topic:

Nawijn et al <https://www.embopress.org/doi/10.15252/msb.20209841>

Contact: Dr Cecilia Lindskog cecilia.lindskog@igp.uu.se

Tel: +46 70 167 98 93

About

Human Protein Atlas

The Human Protein Atlas (HPA) is a program based at the Science for Life Laboratory (Stockholm) and started in 2003 with the aim to map all of the human proteins in cells, tissues and organs using integration of various omics technologies, including antibody-based imaging, mass spectrometry-based proteomics, transcriptomics and systems biology. All the data in the knowledge resource is open access to allow scientists both in academia and industry to freely use the data for exploration of the human proteome. The Human Protein Atlas program has already contributed to several thousands of publications in the field of human biology and disease and it has been selected by the organization ELIXIR (www.elixireurope.org) as a European core resource due to its fundamental importance for a wider life science community. The HPA consortium is funded by the Knut and Alice Wallenberg Foundation. For more information, see: www.proteinatlas.org

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