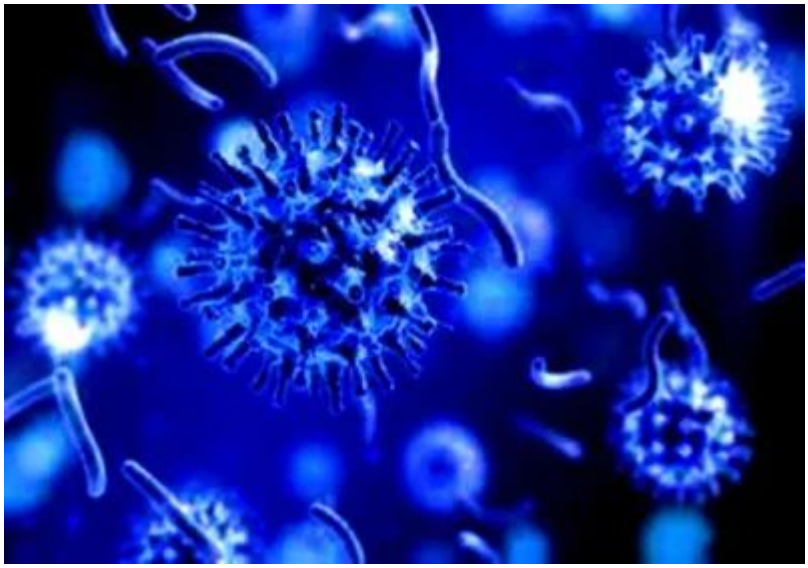
Human endogenous retroviruses (HERVs) are relics of ancient infections, characterized by an RNA intermediate reverse-transcribed into a double-stranded DNA (dsDNA). This dsDNA, called a provirus, can integrate into the genome of the host cell. Because of such endogenization and further fixation in the human population, HERVs have been vertically transmitted to offspring in a Mendelian fashion, constituting up to ~8% of the human genome. HERVs are stable components of the human transcriptome and exhibit differential expression across a diverse range of human tissues. A consortium of authors conducted this study to investigate whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces HERV-W or HERV-K envelope (ENV) protein expression in cultured peripheral blood mononuclear cells (PBMCs) of healthy blood donors, as well as in PBMCs and plasma of COVID-19 patients and *postmortem* tissues obtained from patients deceased from severe acute forms of COVID-19.

Usually, most HERVs are epigenetically silenced or silenced by a mutation, however, under certain conditions, including irradiation, chemical exposures, or exogenous viral factors, they may be activated. When activated by a specific infectious agent, HERVs with pathogenic activity can cause clinical manifestations corresponding to the tissue in which they are expressed. They are considered “dormant enemies within”, and some have significant immunopathogenic and/or neuropathogenic effects *in vitro* and *in vivo.*

Within HERVs, the W group has been extensively investigated for its putative role in several diseases, such as cancer, inflammation, and autoimmunity (for example, in multiple sclerosis). Despite considerable interest in the link between HERV-W expression and the pathogenesis of human diseases, no conclusive correlation has been demonstrated so far. Grandi N, Tramontano E. Viruses. 2017 Jun 27;9(7):162.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5537654/

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein appears to be a major pathogenic factor that contributes to the unique pathogenesis of SARS-CoV-2. Two host-cell factors are important for SARS-CoV-2 viral entry into many cell types: angiotensin-converting enzyme 2 (ACE2), which is bound by S-protein, and transmembrane serine protease 2, which cleaves S-protein, allowing this binding to take place.



***About the study***

The study investigated whether SARS-CoV-2 can activate the expression of the HERV envelope proteins (ENVs) in cultured PBMCs from healthy blood donors, as well as in PBMCs and plasma of COVID-19 patients and *postmortem* tissues obtained from patients deceased from severe acute forms of COVID-19.

*Results*

***SARS-CoV-2 induces HERV-W envelope protein expression in cultures of PBMC from healthy blood donors***

After *in vitro* exposure of PBMCs from healthy blood donors to SARS-CoV-2, PBMCs expressed the HERV-W ENVs in a manner that was independent of the ACE2 receptor, indicating that another undetermined receptor(s) mediated HERV activation by SARS-CoV-2. PBMCs from healthy donors did not express HERV-K ENVs.

The cytofluorometry analysis revealed that early expression of HERV-W ENVs in PBMCs of healthy donors was predominantly and strongly induced in CD3low T lymphocytes within the CD3+T cell population.

The activation of HERVs induced by the SARS-CoV-2 S protein occurred very early after exposure to the virus but before the release of IL-6. This suggests that induction of the

HERV-W ENVs expression was independent of IL-6 production.

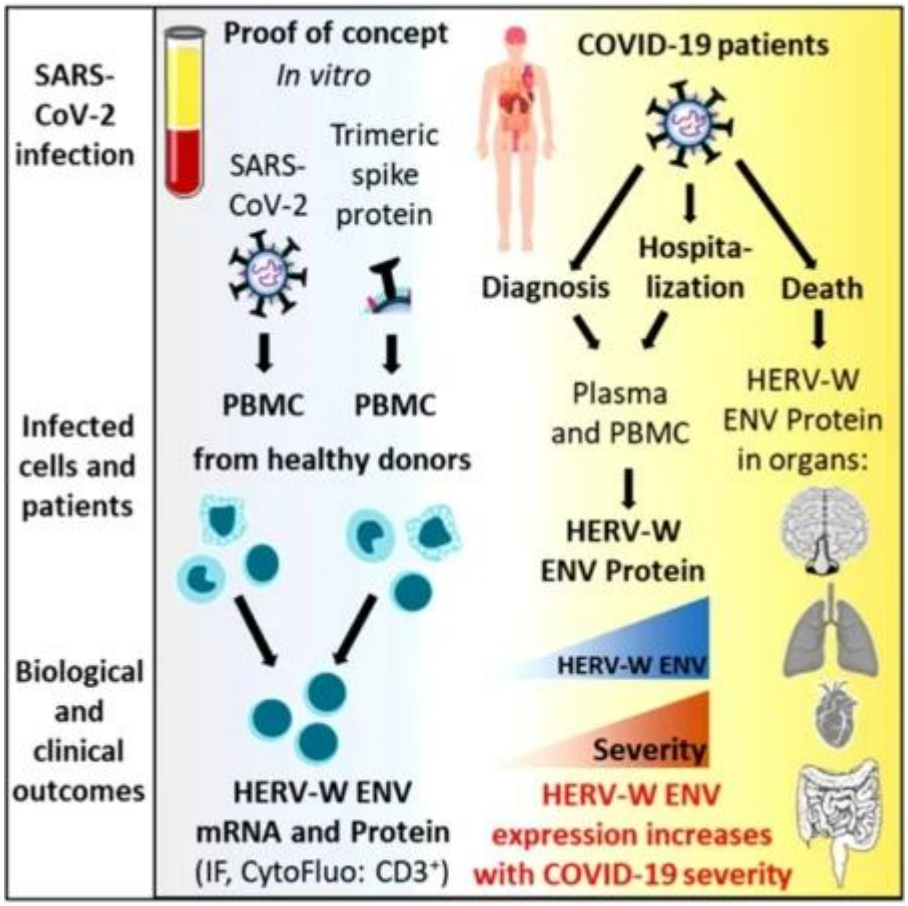



Figure from the original article of Charvet et al. iScience 26,106604 May 19, 2023

### *SARS-CoV-2 induces HERV-W ENV protein expression in plasma and PBMCs of severe COVID-19 patients*

All plasma or serum samples taken from severe COVID-19 patients admitted to the ICU were positive for HERV-W ENV proteins. Furthermore, the mean titer of HERV-W ENVs in plasma progressively increased with disease severity. Since plasma samples of all patients diagnosed with the severe form of COVID-19 were positive for the HERV-W ENVs, the authors suggested that HERV envelope proteins could be a potential marker of COVID-19 severity.

All hospitalized cases with COVID-19, who were positive for the HERV-W ENVs, had lymphopenia. Also, in all hospitalized patients, CD3+T lymphocytes were positive for HERV-

W ENVs. HERV-W ENV proteins were expressed in a significant proportion of CD3low and CD3high T cells and CD19+B lymphocytes. The authors emphasized that the expression of HERV-W was not previously identified in T cells in other pathological conditions.

Cytofluorometry analysis of the blood samples obtained from 21 COVID-19 patients revealed a significant correlation between the plasma levels of soluble HERV-W ENV proteins and the percentage of CD3+T cells positive for HERV-W ENVs.

Interestingly, further analysis conducted in 51 COVID-19 patients demonstrated that proportions of CD3low T lymphocytes positive for HERV-W ENVs were dependent on the SARS-CoV-2 variant. Patients infected with the Omicron variant had a lower proportion of CD3low T lymphocytes positive for HERV-W ENVs. In contrast, CD19+B lymphocytes positive for HERV-W ENVs were the most prevalent in patients infected with the Delta and Omicron variants.

There was no difference in the proportion of CD14+monocytes positive for the HERV-W ENVs between hospitalized COVID-19 patients and healthy blood donors.

Sera from 43 patients diagnosed with other diseases were negative for the HERV-W ENVs and the HERV-K ENVs.

### *HERV-W ENV protein expression in postmortem tissues from severe COVID-19 patients*

*Postmortem* immunohistochemistry analysis was performed on the lung, heart, gastrointestinal tract, nasal mucosa, and brain samples from patients deceased from severe acute COVID-19.

In the lungs and heart, HERV-W ENVs were found in the circulating microthrombi from the lung blood vessels, cardiac muscle, endothelial cells from numerous small blood vessels of the heart, and pericardial fatty tissue. According to these results, the expression of HERV-W ENV proteins in the lungs and heart was closely associated with cells that are involved in COVID-19 pathology, like vasculitis or intravascular thrombotic process. All tissue samples were negative for HERV-K ENVs.

The SARS-CoV-2 N antigen was detected in epithelial cells but not in alveolar macrophages of the lung samples. The SARS-CoV-2 N antigen was not detected in cardiac tissues.

In the gastrointestinal tract, the HERV-W ENVs were found in intestine mucosa and lymphoid tissue next to SARS-CoV-2-positive areas. SARS-CoV-2 N antigen was found in

epithelial cells, the gastric antral mucosa, around submucosal glands of the intestine, and in immune cells from lymphoid tissue associated with mucosa.

In the central nervous system, specimens were taken from the frontal lobe and areas of the olfactory bulb. The HERV-W ENVs were detected in the nasal mucosa, the endothelium of blood vessels, the olfactory bulb, and the microglial cells of the frontal lobe. The HERV-W ENV expression in microglia was confirmed by immunostaining with the antibody against Iba-1. SARS-CoV-2 N antigen was detected in sections from nasal mucosa and CNS-nasal tissue interface, but not in the olfactory bulb or the frontal lobe, suggesting viral replication in nasal mucosa, but not in the neighboring CNS areas of the olfactory bulb.

*Conclusion*

This study has shown that SARS-CoV-2 induces the HERV-W envelope protein expression. It seems that HERV-W ENV proteins are not solely biomarkers of COVID-19 severity or evolution, but also possible pathogenic players that may be involved in the immunopathogenic pathways associated with acute COVID-19 infection and post-acute COVID syndrome.

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**Journal Reference**

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