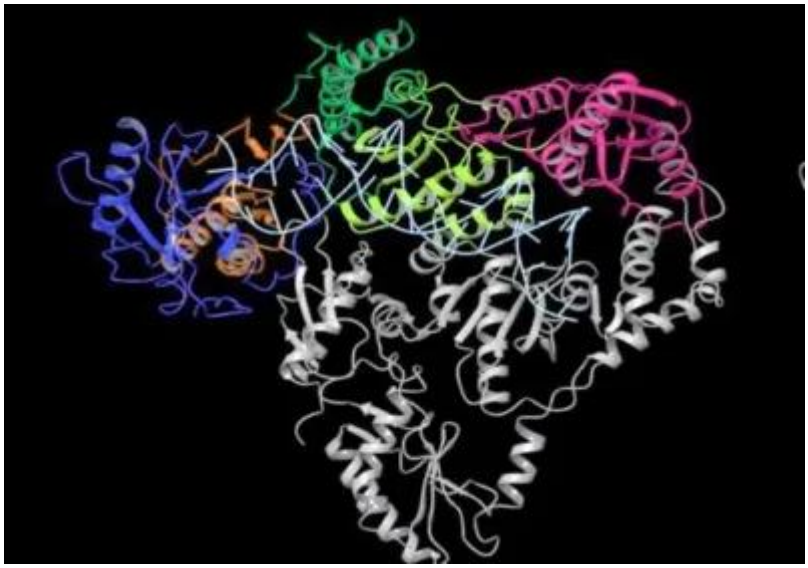
Children positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are usually asymptomatic or develop mild disease. However, they are at risk of developing a postinfectious complication, multisystem inflammatory syndrome in children (MIS-C), characterized by severe systemic inflammation of multiple organs and tissues. Certain clinical characteristics of MIS-C overlap with Kawasaki disease (KD), a febrile systemic vasculitis of the small- and medium-sized arteries that usually affects children under the age of five. Therefore, MIS-C is also called Kawasaki-like syndrome. In this study, researchers from Italy analyzed the transcriptional levels of human endogenous retroviruses (HERVs), HERV-related genes, and immune mediators in children diagnosed with acute COVID-19, acute or subacute KD, acute or subacute MIS-C, and healthy controls.

HERVs are relics of ancient infections, characterized by an RNA intermediate, reverse-transcribed into a double-stranded DNA. This double-stranded DNA, called a provirus, can integrate into the host cell genome. Because of such a process of 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.

Usually, most HERVs are epigenetically silenced or silenced by a mutation. However, they may be activated under certain conditions, including irradiation, chemical exposures, or exogenous viral factors. The aberrant expression of HERVs has been associated with conditions such as infectious, autoimmune, malignant, and neurological diseases. Therefore, HERVs are regarded as “dormant enemies within”.

The authors noted that their research group and other scientists have demonstrated before that SARS-CoV-2 can activate HERVs, inducing inflammatory and immune reactions. A recent study has shown that SARS-CoV-2 can activate HERV-W envelope (*env*) proteins in cultured peripheral blood mononuclear cells of adult healthy blood donors. Circulating HERV-W *env* proteins were detected in plasma or serum samples of adult patients with severe COVID-19 admitted to the ICU and in various *postmortem* tissues obtained from patients who died of severe COVID-19, including the lungs, heart, brain, nasal mucosa, and gastrointestinal tract.
https://discovermednews.com/sars-cov-2-can-induce-expression-of-human-endogenous-retroviruses-w-envelope-proteins/



HERV

About the study

This multicenter prospective study included children diagnosed with the acute or subacute phase of KD, the acute or subacute phase of the MIS-C, the acute COVID-19, and healthy controls. Reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs and symptoms compatible with COVID-19 were used for SARS-CoV-2 infection diagnosis. The diagnosis of KD was made according to the guidelines of the American Heart Association in 2017. The diagnosis of MIS-C was made according to WHO criteria. The "acute phase" was defined as the time from disease onset to the 10th day of fever, while the "subacute phase" was defined as the time from the 11th to the 20th day after the fever onset. The healthy controls reported no neurological or psychiatric disorders or the presence of ongoing infections in their medical history.

The authors used qRT-PCR to assess the transcriptional levels of HERVs, HERV-related genes such as syncytin (Syn) 1 and 2, alanine/serine/cysteine/threonine-preferring transporter (ASCT) 1 and 2, major facilitator superfamily-domain containing 2A (MFSD2A), as well as mRNA levels of inflammatory and regulatory cytokines, such as interleukin (IL)-1β, IL-6, and IL-10, tumor necrosis factor-α (TNF-α), interferon (INF-γ), monocyte chemoattractant protein 1 (MCP-1), and Toll-like receptors (TLR)-3, TLR-4, TLR-7. and TLR-9.

Results

The study included 54 pediatric patients and 19 healthy controls. Eight children were

diagnosed with KD, 17 with MIS-C, and 10 with acute COVID-19.

HERV-W, HERV-K, Syn-1, and ASCT-1 and 2 were upregulated in the blood samples of pediatric patients diagnosed with any of three diseases compared to healthy controls. They also had higher mRNA levels of IL-1β, IL-6, IL-10, TNF-α, MCP-1, IFN-γ, and TLRs than healthy controls.

Children with acute COVID-19 and children in the acute or subacute phase of MIS-C had increased mRNA levels of TLR-3, TLR-4, and TLR-9. These results show that in children diagnosed with COVID-19 or MIS-C, an increase in TLR levels parallels HERV activation.

Only pediatric patients diagnosed with MIS-C had increased transcriptional activity of Syn-2 and MFSD2A. Additionally, only in patients diagnosed with MIS-C, mRNA levels of inflammatory and regulatory cytokines correlated with HERV upregulation. C-reactive protein levels correlated positively with HERV-W expression, whereas IL-10 levels correlated negatively with Syn-2 and HERV-W expression and positively with HERV-K expression.

The progression of MIS-C from the acute to the subacute phase of the disease led to a decrease in TNF-α, TLR-3, TLR-4, TLR-7, and TLR-9 levels and an increase in IL-6 and IL-10 levels. During the progression of KD, TNF-α, MCP-1, and IL-10 levels decreased, and the expression of HERV-K increased.

Comparison between groups

Some children infected with SARS-CoV-2 are at risk of developing a postinfectious MIS-C. Therefore, researchers compared the blood samples of children with these two diseases, as well as the blood samples of children diagnosed with MIS-C with those diagnosed with KD.

Pediatric patients with MIS-C had higher expression of HERV-W, Syn-1 and Syn-2, ASCT-1 and 2, MFSD2A, and TNF-α than children diagnosed with COVID-19. In contrast, pediatric patients with acute COVID-19 had higher IL-6, IL-10, MCP-1, TLR-3, and TLR-9 levels than patients with MIS-C.

Children in the acute phase of MIS-C had higher expression of HERV-W, HERV-K, Syn-1, Syn-2, ASCT-1, MFSD2A, and TNF-α than children in the acute phase of KD. Also, children in the subacute phase of MIS-C had higher expression of HERV-K, Syn-2, MFSD2A, IL-10, and MCP-1 than children in the subacute phase of KD.

Conclusion

This study has shown differences in the upregulation of HERVs, HERV-related genes, and immune mediators in children diagnosed with acute COVID-19, acute or subacute KD, and acute or subacute MIS-C.

The authors emphasized that this study has demonstrated, for the first time, that HERVs and Syn-1 were highly expressed in KD patients, although these levels do not reach those observed in MIS-C. Given the inflammatory nature of KD and the ability of HERVs to modulate the inflammatory response, researchers speculated that HERVs may contribute to the immunopathogenesis of KD.

These findings support the role of HERVs in inflammatory diseases and their interaction with the immune system.

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