Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

HERV-W envelope expression in blood leukocytes as a marker of disease severity of COVID-19

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We are currently in the midst of a pandemic, caused by SARS-CoV-2, that has shaken the entire social and economic fabric of society. Within less than a year it spread across the entire globe and has spared no country, society, race or age group. Even several world leaders have been infected. While we have made great progress towards developing effective vaccines, to date we do not have any effective anti-viral agents. This desperate situation has called for desperate measures. For example, hydroxychloroquine was initially used for treating the infection based on minimal in vitro data, resulting in world-wide shortages of the drug, only for subsequent clinical trials to show that it was ineffective in treating the infection. It has become clear however, that in the early phases of the infection particularly in hospitalized patients, anti-inflammatory measures such as the use of corticosteroids can be helpful. All the same, potent immunosuppression can be detrimental to the host since this is what is necessary for the ultimate recovery of the patient. Hence better methods are necessary that would modulate the immune system more precisely to prevent organ damage and yet preserve the antiviral effects.

The current study by Balestrieri et al. in *EBioMedicine,* studied 30 hospitalized patients infected with SARS-CoV-2 with a wide range of severity of illnesses. They were classified as asymptomatic, presymptomatic, mild, moderate or severe. 24/30 patients were males. They determined the expression of the envelope protein of an endogenous retrovirus family W (HERV-W), in blood leukocytes and compared it to other immune markers and the clinical status of the individuals [1]. The expression of HERV-W envelope protein has been previously implicated in certain autoimmune diseases, such as multiple sclerosis (MS), chronic inflammatory demyelinating polyneuropathy and type 1 diabetes. Increased levels of HERV-W transcripts have also been found in schizophrenia and bipolar disorder [2].

HERVs are retroviral elements derived from retroviruses that infected the human ancestral genome millions of years ago and were incorporated into the chromosomal DNA. Over the years they have become highly mutated; however, several of these genes still have an open reading frame (ORF). Even though there are 22 complete HERV-W families in the human genome, an ORF for the envelope protein is only present in chromosome 7q21.2 [3,4]. The expression of this protein is tightly regulated. It is highly expressed in the human placenta in syncytiotrophoblasts where it is critical for syncytial formation. For this reason, the protein is also called syncytin [5]. However, the protein is epigenetically silenced in the fetus and in adulthood. Reactivation of the gene following thymic development can result in an inflammatory or an autoimmune response. Some viral and bacterial infections have been shown to increase the expression of HERV-W env.

The authors of the present study found that HERV-W envelope can also be activated in patients with COVID-19. They found activation of this protein in circulating *T* lymphocytes. The highest activation was found in CD4 and CD8 lymphocytes with lower levels in *B* cells and monocytes. Previous studies have identified expression of HERV-W in patients with multiple sclerosis in monocytes, NK cells and *B* cells and in *T* cells [6,7]. Increased expression of HERV-W, especially in monocytes, was previously described in acute infections, and importantly, it is associated with an activated phenotype of leukocytes and occurs early upon antigenic stimulation [7].

It is remarkable that exposure of leukocytes in vitro to the SARS-CoV-2 spike protein resulted in a potent and sustained expression of HERV-W envelope. The expression of HERV-W transcripts in leukocytes of patients with COVID-19 corelated with the expression of several proinflammatory cytokines such as IL-6, IL-17 and TNF-α as well as chemokines CCL-2 and CXCL6. These molecules are associated with severe forms of COVID-19 and are poor prognostic markers. In line with this observation, the expression of HERV-W envelope transcripts in leukocytes and protein in CD4 lymphocytes was associated with severe respiratory illness and systemic markers of disease severity. This is important since acute respiratory distress syndrome with COVID-19 is thought to be mediated by an over-aggressive immune response. Further, the antiviral responses to SARS-CoV-2 are primarily mediated by CD4 lymphocytes and not by CD8 cells which may be functionally impaired in some patients [8]. Hence it would be important to determine the effect of HERV-W envelope expression on the functional properties of CD4 lymphocytes.

A previous study identified three different immunophenotypes of hospitalized COVID-19 patients. Immunophenotype 1 showed robust

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CD4 *T* cell activation, paucity of cT_{FH} cells with exhausted CD8 *T* cells. This phenotype was associated with more severe disease. Immunophenotype 2 showed more traditional effector CD8 *T* cells subsets, less CD4 *T* cell activation and immunophenotype 3 showed lack of *T* or B cell activation showing an inability to mount an immune response to the virus [9]. The current study found a correlation between HERV-W envelope expression and *T* cell exhaustion markers suggesting that it might be a driver of immunophenotype 1. Further studies are needed to determine the mechanism of interactions between HERV-W and these molecules. While in vitro studies can provide some insight, human in vivo studies will be necessary since HERV-W expression is specific for humans.

A major question that needs to be answered is, what are the therapeutic implications of these observations? A humanized IgG4 monoclonal antibody to HERV-W envelope, GNbAC1, has already been developed and clinical studies have been conducted in patients with multiple sclerosis and type 1 diabetes. Hence the safety profile is known at least in the context of these phase 1 and 2 studies where the antibody seemed remarkably safe [10]. This might represent an excellent opportunity to conduct a randomized controlled clinical study in patients with COVID-19 to determine if it may provide any benefit to hospitalized patients who are severely ill.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose

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Contributions

Both authors wrote the commentary.

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