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EXPRESSION OF THE PATHOGENIC HERV-W ENVELOPE IN T LYMPHOCYTES IN ASSOCIATION WITH THE RESPIRATORY OUTCOME OF COVID-19 PATIENTS

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Aim: The identification of early biomarkers for predicting coronavirus disease 2019 (COVID-19) progression and of new therapeutic intervention for patient management are needed, considering that no standard therapeutic approach has been established yet. As recent findings that the Human Endogenous Retrovirus-W Envelope (HERV-W ENV) is activated in response to infectious agents and leads to various immune-pathological effects, the present study aimed to evaluated HERVs involvement during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Methods: HERV-W ENV expression in blood samples of COVID-19 patients and Healthy Donors (HDs) was analyzed by flow cytometry and quantitative RT-PCR, and was correlated with clinical signs, inflammatory markers, cytokine expression, and disease progression. To address the contribution of SARS-CoV-2 on the activation of HERV-W ENV, *in vitro* experiments were performed stimulating Peripheral Blood Mononuclear Cells (PBMCs) from HDs with SARS-CoV-2 Spike protein and monitoring the induction of HERV-W ENV and IL6 expression after 3, 24 h and 5 days. Results: HERV-W ENV has been found expressed both as mRNA and protein, in blood samples from COVID-19 but not in HDs. A high percentage of HERV-W ENV positive leukocytes has been found in COVID19 patients. Lymphocytes displayed the highest values among all leukocytes, and in particular, $CD3^+$ T cells showed the highest percentage of HERV-W ENV positive cells. HERV-W ENV expression correlated with the T cell differentiation, exhaustion, and senescence markers: in particular, in $CD3^+CD8^+$ T HERV-W ENV expression was associated with a decrease in naïve ($CD45RA^+CCR7^+$) and central memory ($CD45RA^-CCR7^+$) cells and positively correlated with effector memory ($CD45RA^-CCR7^-$) and terminal effector memory (CD45RA+ CCR7-) cells. Furthermore, HERV-W ENV positively correlated with $CD3^+CD4^+PD1^+$ and $CD3^+CD8^+CD57^+$ T cells. Moreover, the percentage of HERV-W ENV-positive cells in $CD4^+$ T cells significantly correlated with coagulopathy markers and biochemical parameters associated with COVID-19 severity. Interestingly, a significant increase in the percentage of HERV-W ENV-positive lymphocytes across groups with different pulmonary involvement was observed. Finally, by *in vitro* stimulation with SARS-CoV-2 Spike protein of PBMCs of HDs, an early mRNA production of HERV-W ENV was already observed at 3h, and ahead of the induction of IL6 which was significantly detected from 24h onwards. After 5 days, a significant increase in the percentage of CD3+ HERV-W ENV positive cells was observed by flow cytometry. Discussion: The data demonstrated a close association between the expression of HERV-W ENV and several immunological and clinical markers related to the severity of COVID-19 disease. Conclusion: The obtained data support the role of HERV-W ENV as contributing factor in the development and progression of COVID-19 and candidate it as a new potential therapeutic target.