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Extracellular vesicles from bone marrow (MSC-EVs) and adipose (ASC-EVs) mesenchymal stem cells protect lung epithelial-endothelial barrier after challenge with plasma from severe COVID-19 ARDS patients.

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BACKGROUND: ARDS induced by SARS-CoV-2 has high mortality and few treatments are available. Stem-cell derived extracellular-vesicles (EVs) are emerging as a possible therapeutic strategy.

OBJECTIVE and HYPOTHESIS: Plasma from severe COVID-19 ARDS patients induces oxidative stress and damage on lung epithelial-endothelial barrier. Extracellular-vesicles from bone marrow (MSC-EVs) and adipose (ASC-EVs) mesenchymal stem-cells mitigate these injuries.

METHODS: BEAS-2B and HMEC cells were used as lung barrier model. We tested 5 plasmas of healthy volunteers and 10 plasmas of COVID-19 ARDS patients treated whit VV-ECMO.
BEAS-2B and HMEC were seeded in chamber slides and multiwell plates and challenged with plasma of healthy volunteers or COVID-19 patients. MSC-EVs or ASC-EVs were added simultaneously with plasma or after 6 hours. After 24 hours, we evaluated the expression of tight junction proteins ZO-1 and Occludin by immunofluorescence, as well as oxidation parameters (total and mitochondrial ROS concentration, lipid peroxidation, GSH and GSSG) and antioxidant enzymes activity (SOD1, SOD2, TXNRD1, GSR, GPX). Mann-Whitney test was performed for statistical analysis.

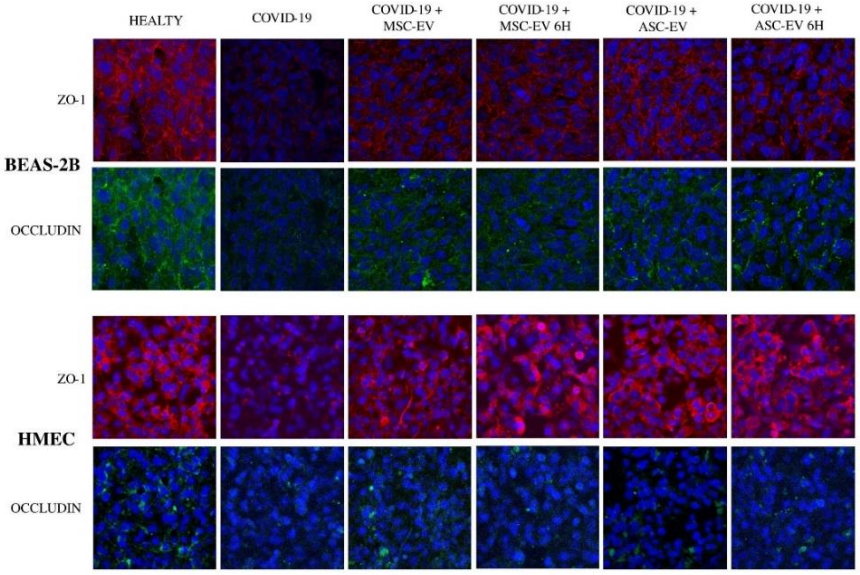

Fig. 1. Representative images of ZO-1 and Occludin expression in BEAS-2B and HMEC cells. Plasma of severe COVID-19 induced loss of tight junction proteins expression. MSC-EVs and ASC-EVs mitigate this effect when they are added simultaneously with plasma or after 6 hours. COVID-19 plasmas tested n=10 for BEAS-2B n=5 for HMEC.

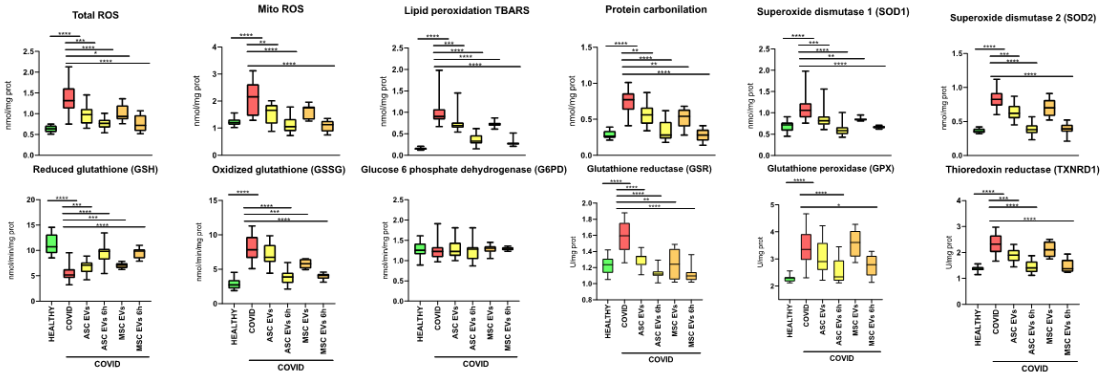

Fig. 2 Oxidative Stress Parameters and Antioxidant Enzymes Activity. All show significant increase with COVID -19 plasma challenge in BEAS 2B cells. The addition of both ASC and MSC EVs drastically decrease oxidative stress, especially when added 6 hours after plasma. COVID-19 plasmas tested n=10

RESULTS: COVID-19 plasma significantly attenuated the expression of ZO-1 ($p<0,0001$) and Occludin ($p<0,0001$) compared to the healthy control in both BEAS-2B and HMEC cells, while it increased all oxidation parameters ($p<0,001$) and the activity of all studied antioxidant enzymes ($p<0,001$) (Figure 1). MSC-EVs and ASC-EVs added together with COVID-19 plasma or after 6 hours restored the expression of ZO-1 (MSC-EVs $p<0,0001$; ASC-EVs $p<0,0001$) and Occludin (MSC-EVs $p=0,0019$; ASC-EVs $p=0,0002$) in BEAS-2B and HMEC cells. The addition of ASC-EVs to BEAS-2B cells added both simultaneously and after 6 hours was able to restore redox balance (Figure 2).

CONCLUSIONS: Plasma of severe COVID-19 ARDS patients induces damage and oxidative stress in a cellular model of lung epithelial-endothelial barrier. MSC-EVs and ASC-EVs mitigate this injury when they are added together or after 6 hours, suggesting their potential therapeutic effect.