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基礎科学

Mesenchymal stem cell-derived extracellular vesicles reduce cellular inflammation responses to respiratory viral proteins

■ はじめに

Several studies have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is co-infected with the influenza virus (IAV) and is associated with disease severity and mortality (1). Therefore, it is necessary to investigate the co-impact of SARS-CoV-2 and IAV on lung function and develop effective therapeutic strategies for the treatment of influenza patients with post-COVID-19 syndrome.

Extracellular vesicles derived from Wharton's jelly mesenchymal stem cells (WJ-EVs) hold promising therapeutic potential due to their immunomodulatory and anti-inflammatory properties, as they contain biological signals such as proteins, mRNAs, and miRNAs that can be transferred to target cells to modulate their genotypic and phenotypic characteristics. Numerous studies have reported the role of WJ-EV in improving severe lung injury induced by bacteria or viruses (2). However, the effects of WJ-EV treatment on SARS-CoV-2 and IAV co-infection have not been elucidated. In the present study, we examined the effects of co-induction of SARS-CoV-2 and H1N1 viral proteins on lung epithelial-endothelial cell crosstalk and the ability of WJ-EV to rescue these alterations.

■ 活動内容

1. Method

Lung epithelial cells (EpiC) were co-induced using the SARS-CoV-2 S-protein and the H1N1 HA protein for 24 hours, followed by treatment with WJ-EVs for an additional 24 hours. After the treatment, cytokine secretion was analyzed using an ELISA kit, while the levels of the p65 protein were examined using a western blot. The conditioned medium (CM) was then collected for future experiments. Lung endothelial cells (EC) function was assessed after treatment with the CM from the co-induced lung EpiC. The expression levels of angiogenesis-related genes were analyzed using quantitative PCR. To investigate the underlying mechanism, miRNA sequencing analysis was performed, followed by predictive analysis using various database tools. Finally, to confirm these predictions, inhibitory and mimic assays were carried out.

2. Results

Viral protein co-induction resulted in a robust upregulation of inflammatory cytokines in lung EpiC compared to single inductions. Consequently, viral protein-co-induced lung EpiC exhibited altered effects on the epithelial-endothelial crosstalk, which induced apoptosis and impaired the angiogenic abilities of lung ECs. Of note, WJ-EVs transferred miR-146a to the recipient lung EpiC, which impaired TRAF6 and IRAK1, resulting in the downregulation of the NF-κB pathway and secretion of inflammatory cytokines, and rescuing the epithelial-endothelial crosstalk. Our findings suggested that WJ-EVs provide an encouraging insight into developing an inventive approach to regulate inflammatory cytokines induced by co-infection of both SARS-CoV-2 and H1N1 influenza viruses.

■ 関連情報等(特許関係、施設)

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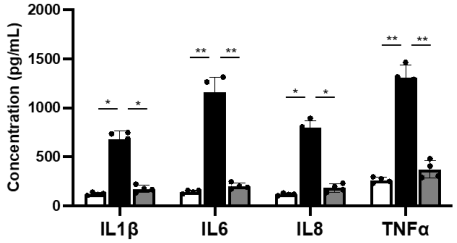

Figure 1. WJ-EVs treatment suppressed the elevation of cytokine secretion in lung EpiC co-induced by SARS-CoV-2 S-protein and H1N1 HA protein

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■キーワード: (1) Extracellular Vesicles
(2) Mesenchymal Stem Cells
(3) SARS-CoV-2