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Efficacy of mesenchymal stem cell (MSC)-derived extracellular vesicles (EVs) in cisplatin nephrotoxicity using three-dimensional gravity-driven two-layer tubule-on-a-chip (3D-MOTIVE chip)

EUNJEONG KWON
Seoul National University Bundang Hospital, Korea, Republic of

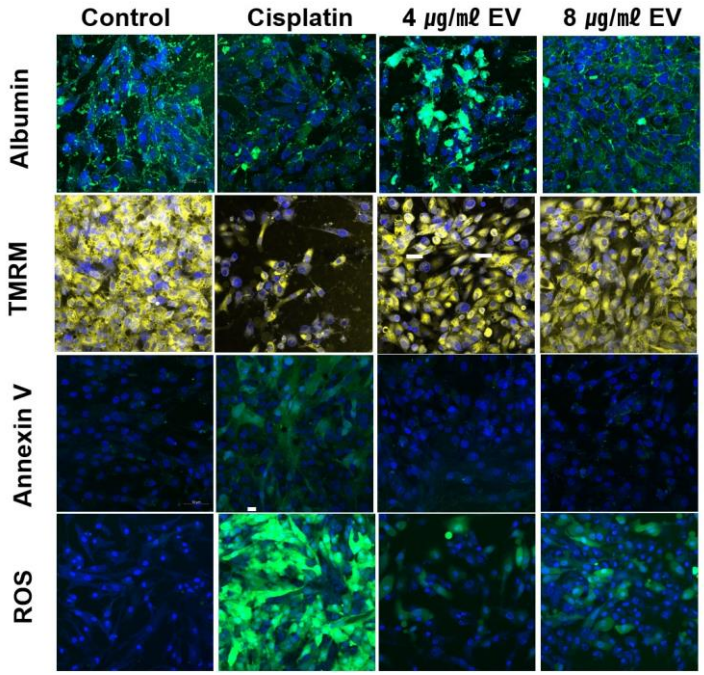
Objectives: Mesenchymal stem cells (MSCs)-derived extracellular vesicles (EVs) are known to have a therapeutic effect on nephrotoxicity. Animal models require a large amount of EV to evaluate the effect, and there is a need for a new experimental technique that can accurately predict the effectiveness in humans. We evaluated the therapeutic effect of MSCs-derived EVs in cisplatin nephrotoxicity using a three-dimensional gravity-driven two-layer tubule-on-a-chip (3D-MOTIVE chip).

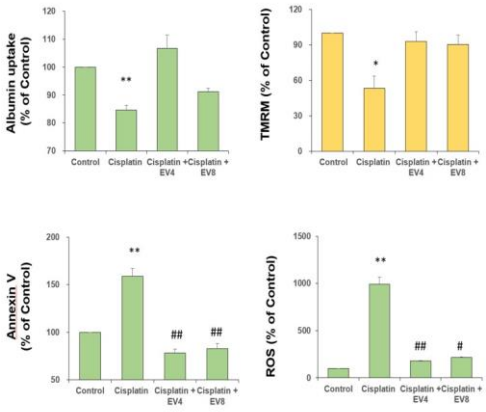
Methods: We cultured renal proximal tubular epithelial cells (RPTEC) on the bottom and glomerular endothelial cells (GMVECs) on the top side of the insert device. Furthermore, we transferred the insert device to the bottom plate of the 3D-MOTIVE chip. We designed the flow rate to the 3D-MOTIVE chip at an angle of 7° and intervals of 8 min using a rocker at 37 °C. We introduced cisplatin 10mM into the chips for 24 hours, replaced the medium, and treated 4μg/ml and 8μg/ml of EVs over 24 hours. We evaluated functionality by albumin uptake and tetramethylrhodamine methyl ester (TMRM) assay and viability by Annexin V and reactive oxygen species (ROS).

Results: In the 3D-MOTIVE chip, cisplatin 10μM decreased attached cells, TMRM, and albumin uptake compared to the vehicle. Conversely, Annexin V and ROS increased. After EVs 4μg/ml and 8μg /ml were treated, cell viability increased 2.8-fold and 2.5-fold, respectively, compared to the cisplatin-induced nephrotoxicity group. It also increased cell attachment 2.25-fold in EVs 4μg/ml and 2.02-fold in EVs 8μg/ml. Albumin uptake and TMRM increased after EV treatment but not significantly. Otherwise, Annexin V and ROS decreased compared to the cisplatin-induced nephrotoxicity group. There were no differences according to the EV concentration.

Conclusions: We created the cisplatin-induced nephrotoxicity model on the 3D-MOTIVE chip. We found that MSCs-derived EVs have restored cell viability. In the future, MSCs-derived EVs have the potential to ameliorate cisplatin-induced nephrotoxicity.

MSCs-derived EVs effect on 3D-MOTIVE chip





- Specificity

*p < 0.05, **p < 0.01 vs. Control

#p < 0.05 , ##p < 0.01 vs. Cisplatin