Human embryonic stem cell-derived mesenchymal stem cells improve mitochondrial oxidative dysfunction in metabolic dysfunction-associated liver disease via the AMPK pathway

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EASL CONGRESS Milan, Italy 5–8 June 2024

SNUH SEOUL NATIONAL UNIVERSITY HOSPITAL

Poster Session Online

Introduction

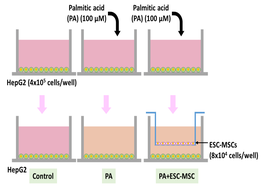
▶ **Metabolic dysfunction-associated liver disease (MAFLD)** is one of the most common chronic liver diseases worldwide, but pathophysiology is not fully understood and pharmacological therapy for MAFLD is not yet available.[1]

▶ Human embryonic stem cell-derived mesenchymal stem cells (ES-MSCs) have the **immune privilege** and are relatively **free from the risk of tumorigenicity**.[2] Therefore, it could be highly applicable for stem cell therapy by compensating for the flaws of embryonic stem cells.

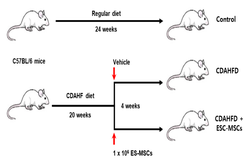
▶ We investigated therapeutic potential of ES-MSCs on hepatic steatosis and mitochondrial oxidative function.

Methods

▶ *In vitro* study
: HepG2 cells + PA → co-cultured with ESC-MSCs (HepG2 : ESC-MSC=5:1)



▶ *In vivo* study
: C57BL/6 mice fed with CDAHFD (choline-deficient, L-amino acid-defined, high-fat diet).[3]
→ At week 20, mice were injected with ESC-MSCs (transplanted; 1 × 10^6 cells).
→ Four weeks later, liver histology and function were assessed.

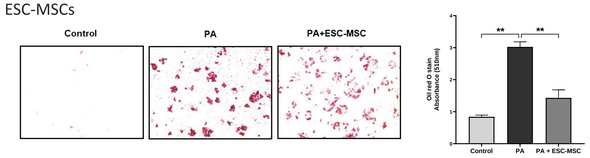


▶ Lipid accumulation was measured through oil red O staining in both cellular and animal models. Mitochondrial mass, reactive oxygen species (ROS), and the activity of antioxidant enzymes were measured to assess mitochondrial oxidative functions.

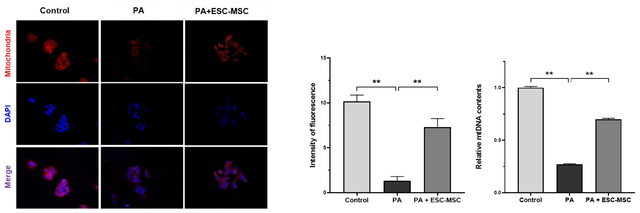
Results

In vitro study

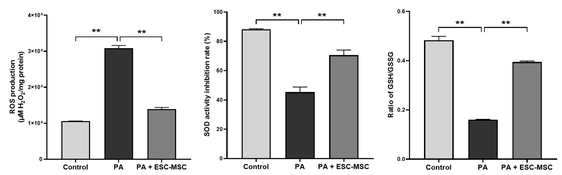
▶ PA-induced intracellular lipid accumulation was attenuated when co-cultured with ESC-MSCs



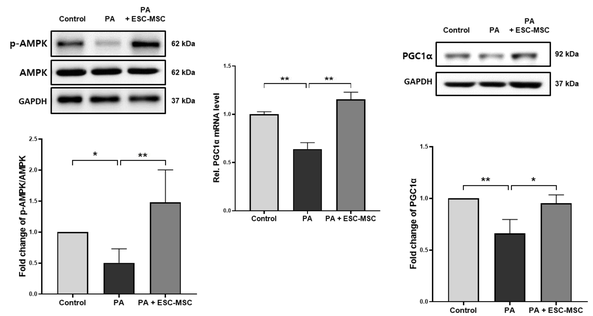
▶ The functional mitochondrial mass and mtDNA contents were reduced by PA treatment and then was restored following co-culture with ESC-MSCs



▶ Increased cellular ROS production by PA treatment was attenuated after co-culture with ESC-MSCs. The activity of SODs and the ratio of reduced/oxidized glutathione were decreased by PA treatment and were restored by co-culture with ESC-MSCs.

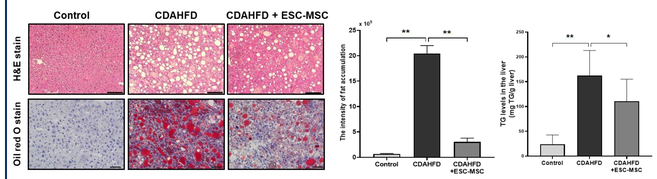


▶ The expression levels of phosphorylated AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator-1 (PGC1α) were significantly increased following co-culture with ESC-MSCs.

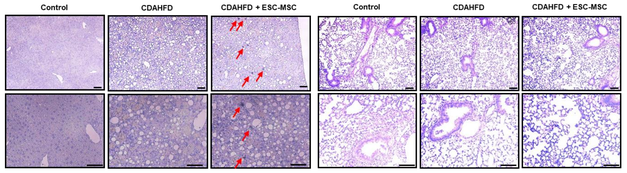


In vivo study

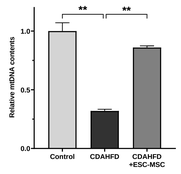
▶ Severe hepatic steatosis in CDAHFD-fed mice was ameliorated following transplantation of ESC-MSCs



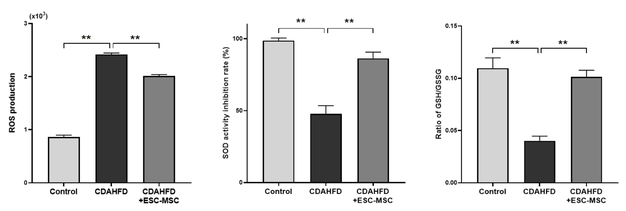
▶ Engraftment of human ESC-MSC into the mouse liver, , rather than the lung was visualized by anti-hHLA immunohistochemistry and immunofluorescence assay.



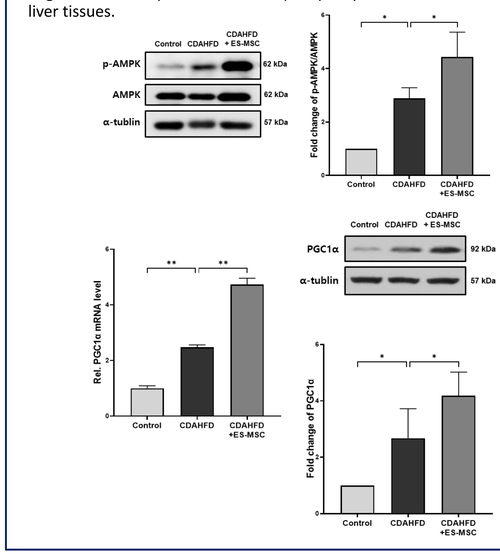
▶ Decreased mitochondrial DNA content in the liver tissues of CDAHFD-fed mice was reinstated to near-control levels after the transplantation of ESC-MSCs.



▶ Augmented hepatic ROS accumulation caused by CDAHFD was attenuated after the transplantation of ESC-MSCs, with dynamic changes in the activity of SOD and the ratio of glutathione.



▶ The transplantation of ESC-MSCs into CDAHFD-fed mice significantly augmented the expression levels of phosphorylated AMPK and PGC1α in the liver tissues.



Conclusion

▶ **Severe hepatic steatosis** and **mitochondrial dysfunction** were observed in cellular and animal models of MAFLD, suggesting that mitochondrial dysfunction might be important for the pathogenesis of MAFLD.
▶ Our pre-clinical results demonstrated that treatment with **ESC-MSCs could ameliorate hepatic steatosis** through the recovery of mitochondrial functions.
▶ These results provide a **therapeutic basis for the use of ESC-MSCs** as a novel treatment option for MAFLD patients.

Reference

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Disclosure

Dr. Lee YB reports receiving research grant from Samjin Pharmaceuticals and Yuhan Pharmaceuticals; Dr. Yoon JH reports grant/research support from Dicerna Pharmaceuticals, Roche, GlaxoSmithKline, AstraZeneca, Daewoong Pharmaceuticals, and Hanmi Pharmaceuticals.

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DOI: 10.3252/pso.eu.EASL2024.2024

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