Human umbilical cord-derived mesenchymal stem cells alleviate autoimmune hepatitis by inhibiting hepatic ferroptosis

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Abstract

Autoimmune hepatitis (AIH) is an immune-mediated liver disease with limited current therapies. Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) show therapeutic potential, but their mechanism in AIH remains unclear. Using a Concanavalin A (ConA)-induced AIH-like mouse model, we evaluated hUC-MSCs' effects and underlying mechanisms via survival analysis, liver function tests, histopathology, metabolomics, and ferroptosis marker detection.

Results

- hUC-MSCs improved survival (all ConA+MSC mice survived 24h vs. 100% ConA-only mortality by 18h), mitigated liver swelling/redness, reduced serum liver function markers (ALP, ALT, AST, TBIL, etc.), and attenuated hepatocyte damage and apoptosis (H&E and TUNEL staining). Lentivirus-labeled hUC-MSCs showed enhanced hepatic homing to injured livers.

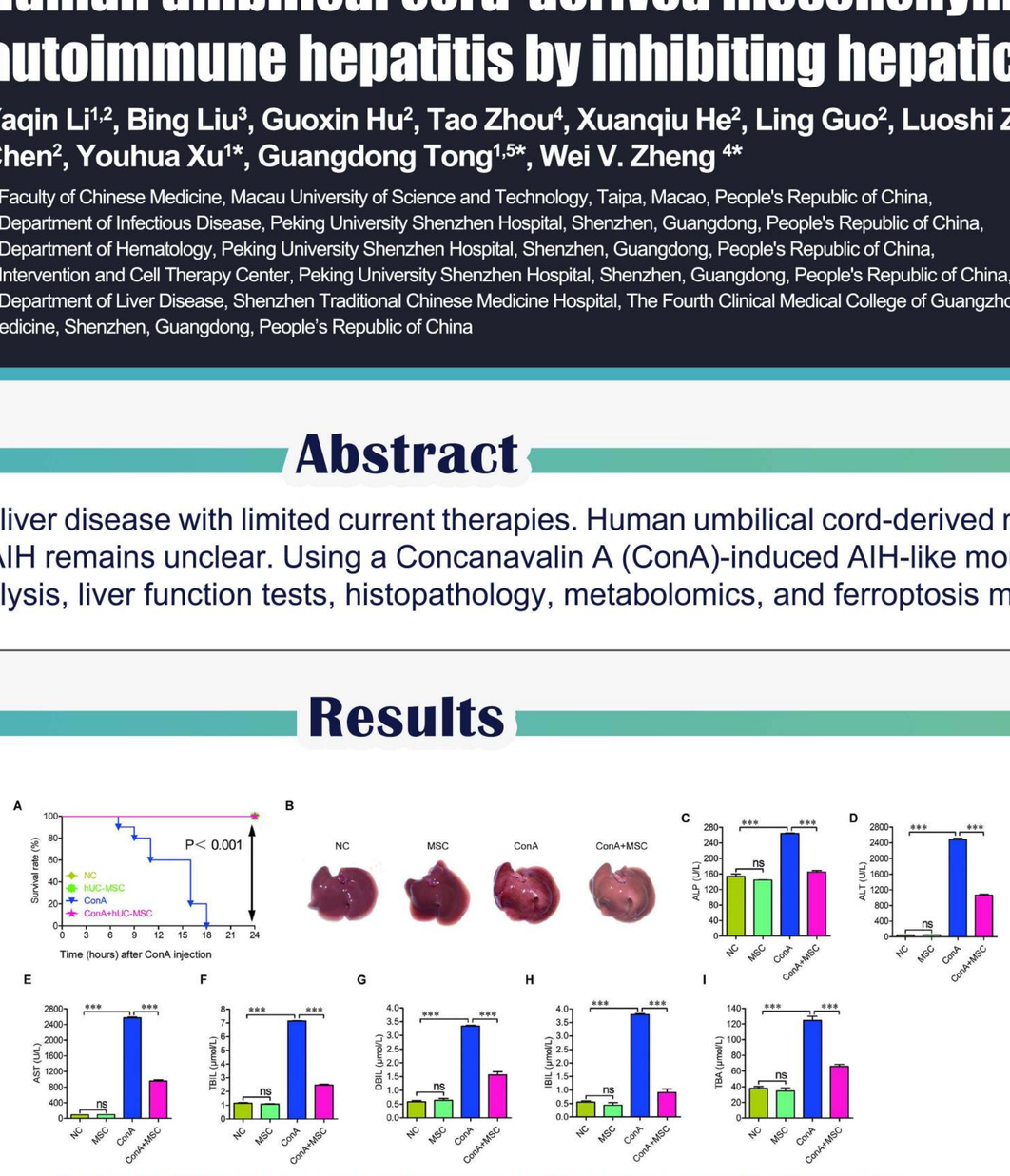

Fig 1. hUC-MSCs improve survival and liver function in ConA-induced AIH-like mice.

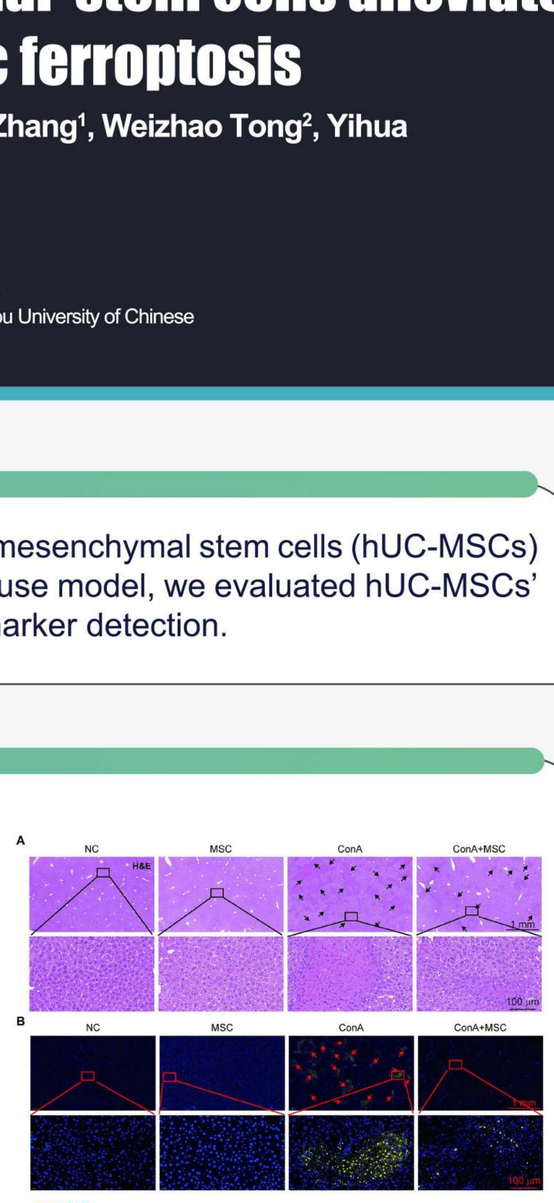

Fig 2. hUC-MSCs alleviate hepatic damage and apoptosis in ConA-injured livers.

- Metabolomic profiling (OPLS-DA) revealed distinct signatures among groups. KEGG analysis identified ferroptosis as a key pathway, with shared differentially expressed metabolites (Glu derivatives, peptides) linked to ferroptosis.

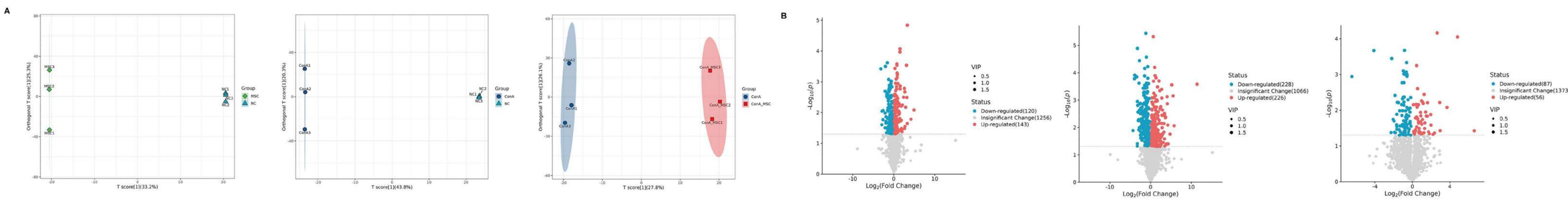

Fig 3. OPLS-DA reveals distinct metabolomic profiles in liver tissues across treatment groups.

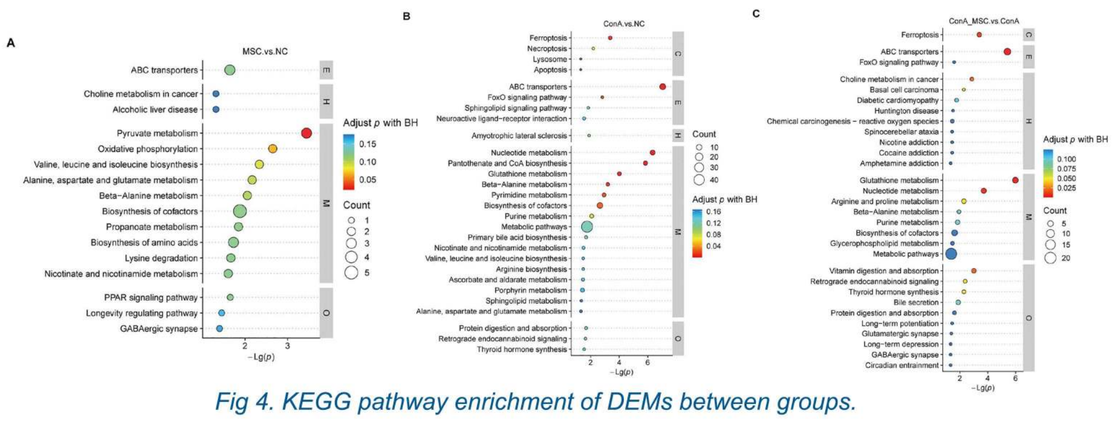

Fig 4. KEGG pathway enrichment of DEMs between groups.

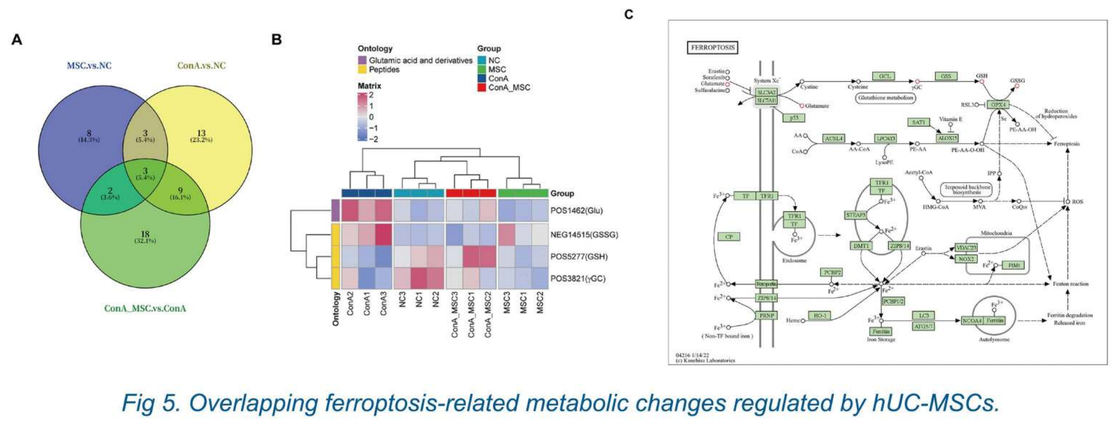

Fig 5. Overlapping ferroptosis-related metabolic changes regulated by hUC-MSCs.

- hUC-MSCs reversed ConA-induced ferroptosis-related changes: reduced MDA, GSSG, Glu, and Fe^{2+}; restored GSH and GSH/GSSG ratio; downregulated COX2 (ferroptosis marker); upregulated SLC7A11, GPX4, and FTH1 (ferroptosis suppressors) at mRNA and protein levels.

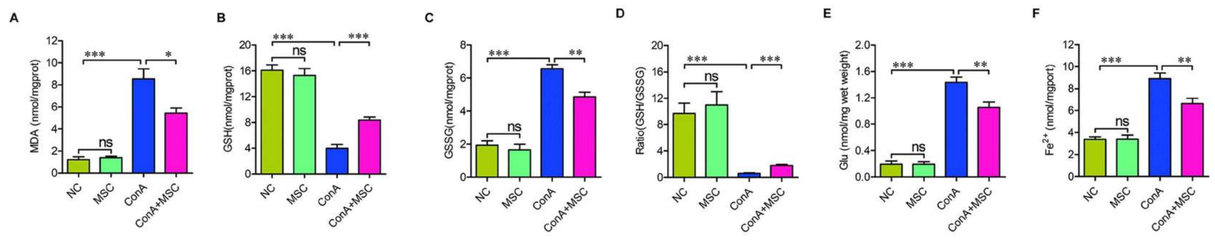

Fig 6. hUC-MSCs reverse ferroptosis-related biochemical changes in ConA-injured livers.

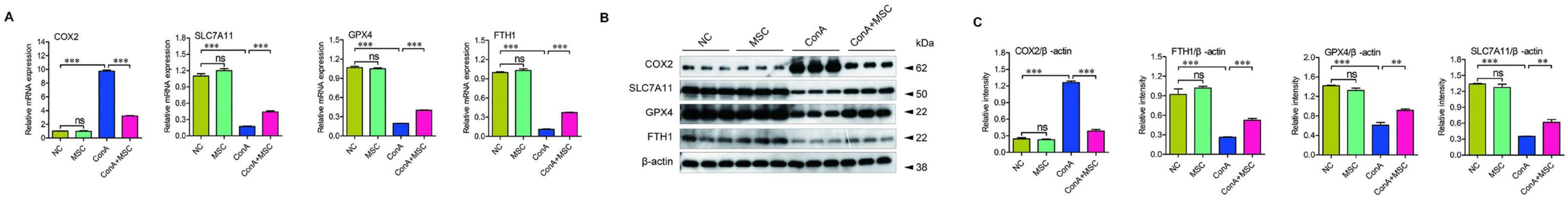

Fig 7. hUC-MSCs regulate expression of ferroptosis-related genes and proteins.

Conclusions

hUC-MSCs alleviate ConA-induced AIH-like liver injury in mice, potentially by modulating ferroptosis-related pathways. Further studies are needed to elaborate detailed regulatory mechanisms, supporting hUC-MSCs as a promising AIH therapy.

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