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Comprehensive Characterization of MSCs-derived Extracellular Vesicles Using Different Culture Media: FBS versus HPL

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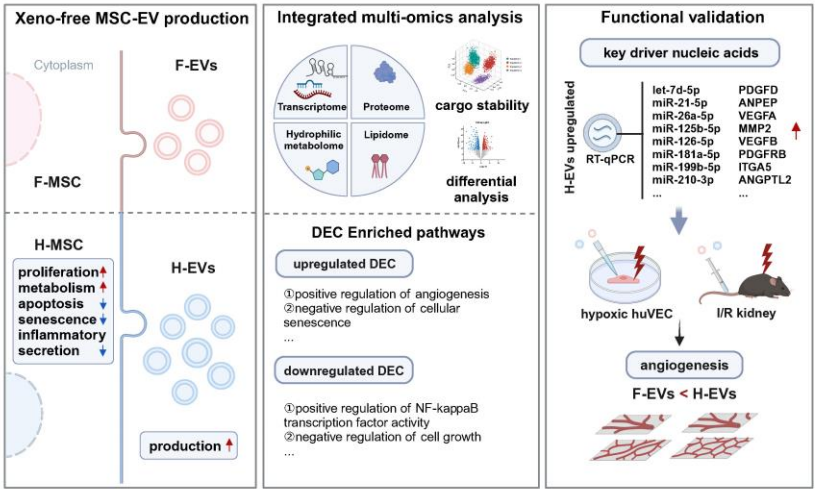
Objectives : Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) have emerged as a promising regenerative therapy. However, the clinical application of MSC-EVs is hindered by the presence of xenogeneic components in fetal bovine serum (FBS), which is commonly used as a culture medium for MSCs. The suitability of platelet lysate (HPL) as an alternative to FBS for culturing MSCs and obtaining EVs for clinical translation remains unclear.
Methods : In this study, we systematically compared the effects of FBS and HPL culture mediums on MSC-EVs using various EV characterization techniques, multi-omics sequencing, and functional validation.
Results : Our findings demonstrated that MSCs cultured under HPL exhibited higher cellular activity and EV production compared to those cultured under FBS conditions. However, the key quality attributes of MSC-EVs showed no significant differences between FBS and HPL culture conditions. Multi-omics analysis revealed that H-EVs derived from various umbilical cord donors exhibited greater stability. Multi-omics sequencing identified differential enrichment of proteins, nucleic acids, and metabolites due to different culture conditions. Notably, upregulated components in H-EVs demonstrated greater regenerative potential, while upregulated components in F-EVs were more prone to eliciting immune responses. Additionally, miRNAs and mRNAs associated with angiogenesis were significantly upregulated in H-EVs, inducing the formation and migration of tube-like structures in human umbilical vein endothelial cells (hucVECs). In vitro and in vivo disease models further demonstrated that compared to F-EVs, H-EVs significantly reduced renal capillary rarefaction in a mouse model of renal ischemia-reperfusion injury and promote the regeneration of hypoxic hucVECs.
Conclusions : In conclusion, our study highlights the differences in EV production, properties, composition, and function under different culture conditions. Building upon previous research on F-EV-based therapeutic studies, our findings suggest the potential of using xenogeneic H-EVs as a safe and effective regenerative therapy.

APCN Figure.jpg


Xeno-free MSC-EV production
Cytoplasm
F-EVs
F-MSC
H-MSC
proliferation
metabolism
apoptosis
senescence
inflammatory
secretion
H-EVs
production
Integrated multi-omics analysis
Transcriptome
Proteome
Hydrophilic metabolome
Lipidome
cargo stability
differential analysis
DEC Enriched pathways
upregulated DEC
①positive regulation of angiogenesis
②negative regulation of cellular senescence
...
downregulated DEC
①positive regulation of NF-kappaB transcription factor activity
②negative regulation of cell growth
...
Functional validation
key driver nucleic acids
H-EVs upregulated
RT-qPCR
let-7d-5p
miR-21-5p
miR-26a-5p
miR-125b-5p
miR-126-5p
miR-181a-5p
miR-199b-5p
miR-210-3p
...
PDGFD
ANPEP
VEGFA
MMP2
VEGFB
PDGFRB
ITGA5
ANGPTL2
...
hypoxic huVEC
I/R kidney
angiogenesis
F-EVs < H-EVs