Mitochondrial therapy promotes chondrogenesis of human adipose tissue derived MSCs under inflammatory stress

Q. Wang[1], P J. Emans[3], L. Moroni [1], B. Cillero-Pastor[1,2]

[1] MERLN Institute for Technology-Inspired Regenerative Medicine, Maastricht University, Maastricht, the Netherlands
[2] The Maastricht Multimodal Molecular Imaging Institute (M4i), Imaging Mass Spectrometry, Maastricht University, Maastricht, the Netherlands
[3] Laboratory for Experimental Orthopedics, Department of Orthopedic Surgery, CAPHRI Care and Public Health Research Institute, Maastricht University Medical Center+, Maastricht, the Netherlands

Introduction

- **Osteoarthritis** (OA) is a degenerative joint condition characterized by cartilage degradation and low-grade, chronic inflammation.
- **Mitochondria** dysfunction has been associated to OA and cartilage degeneration.
- Infrapatellar fat pad–derived mesenchymal stem cells (**IPFP-MSCs**) are a promising cell source for cartilage repair due to their accessibility, multipotency, and active paracrine activity.
- This study explores the potential chondroprotective and anti-inflammatory effects of Elamipretide (**SS-31**), a mitochondria-targeted peptide, in IL-1β-induced hMSCs.

Methods

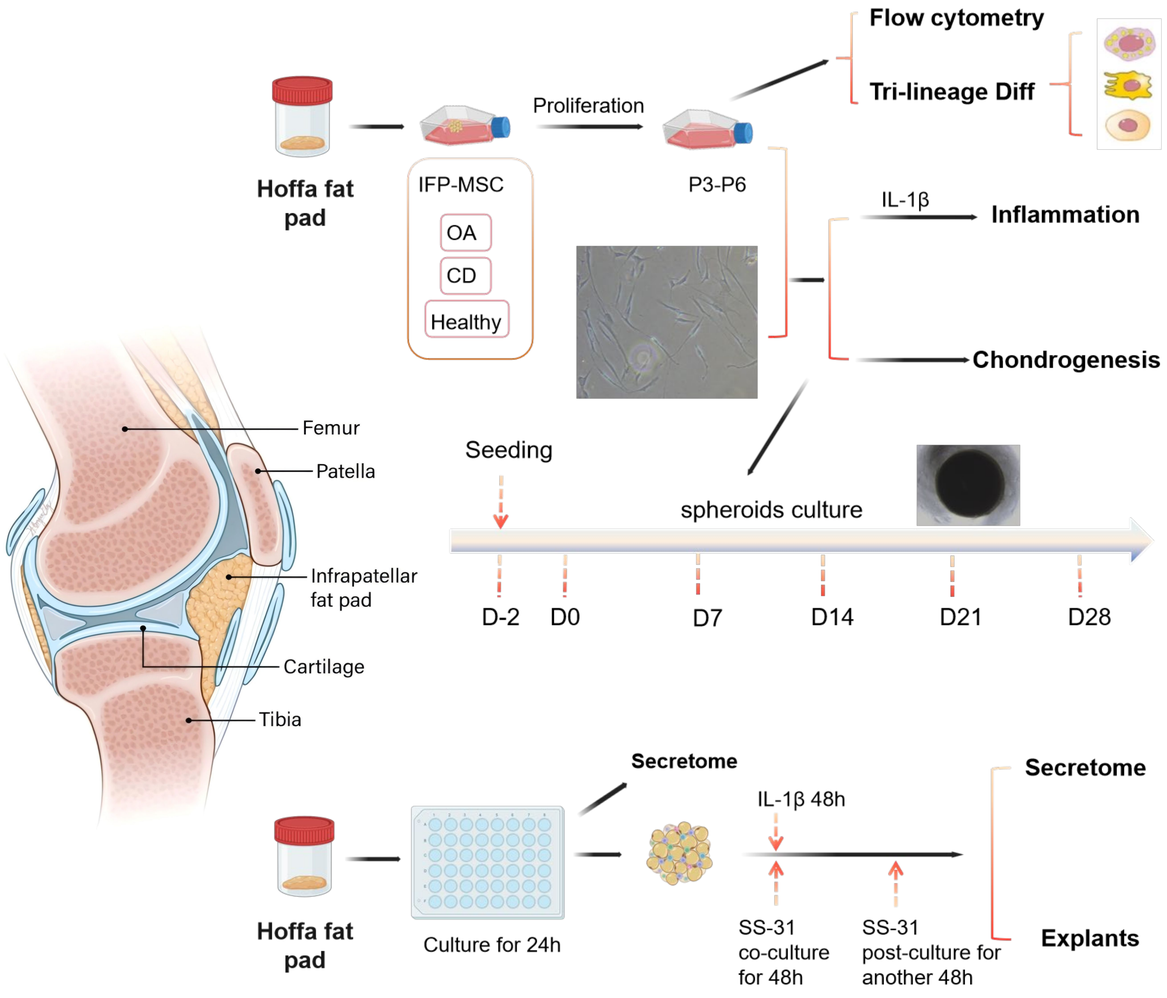


Figure 1. Methodology and model design.

Results

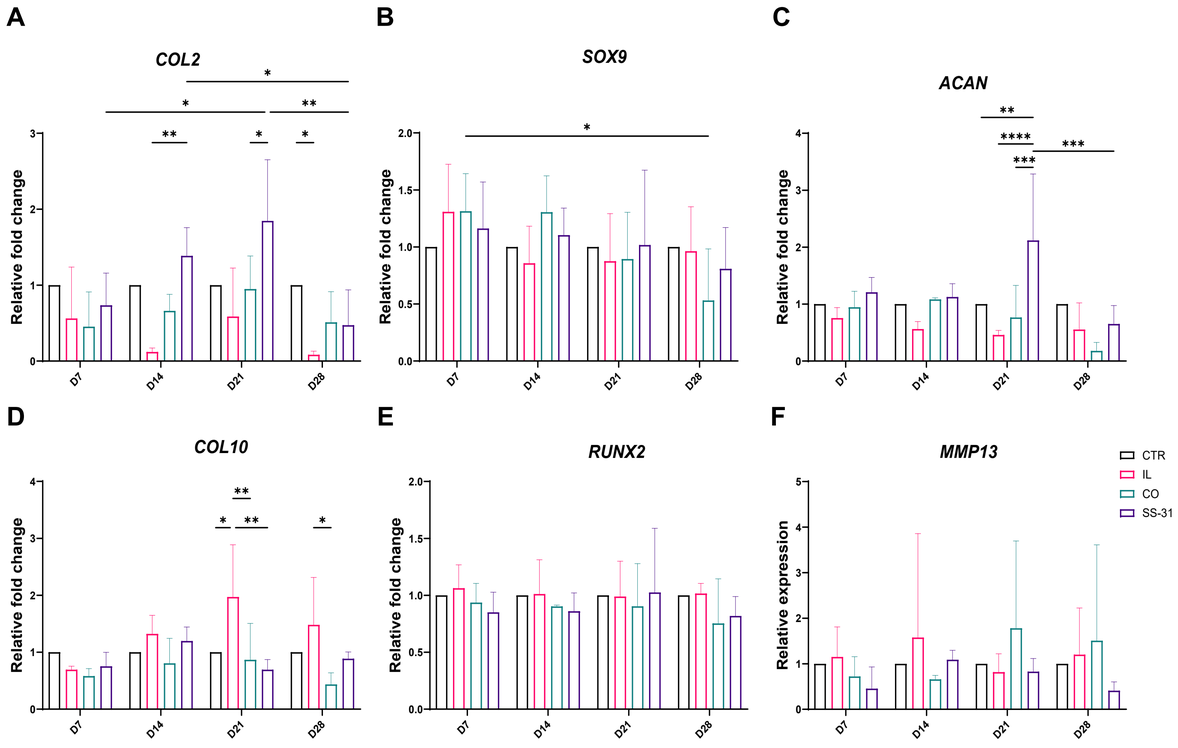


Figure 2. Chondrogenic gene expression during differentiation. Relative mRNA expression of (**A**) *COL2A1*, (**B**) *SOX9*, (**C**) *ACAN*, (**D**) *COL10,* (**E**) *RUNX2 and* (**F**) *MMP13* was evaluated in hMSC pellets cultured with/without IL-1β (10 ng/mL)/SS-31 (25 μM) on days 7, 14, 21, and 28 of chondrogenic differentiation. Data are shown as mean ± SD (*n* = 3 biological replicates, OA donors).

Results

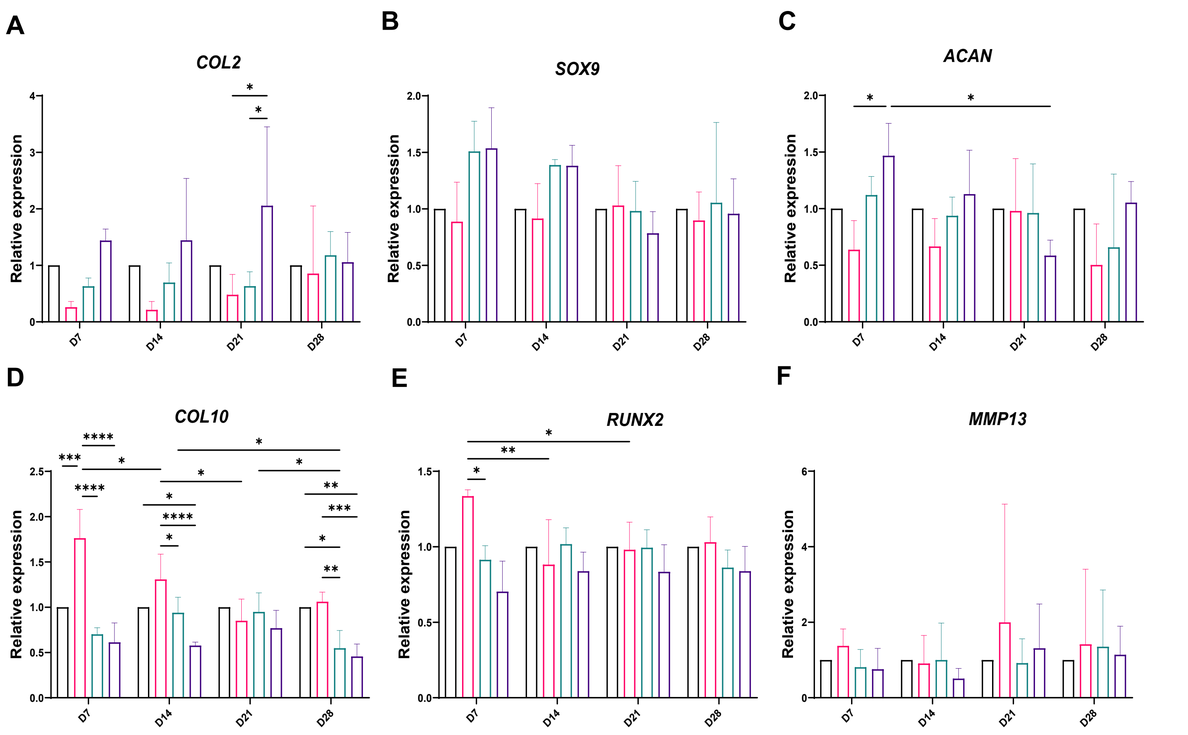


Figure 3. Chondrogenic gene expression during differentiation. Relative mRNA expression of (**A**) *COL2A1*, (**B**) *SOX9*, (**C**) *ACAN*, (**D**) *COL10,* (**E**) *RUNX2 and* (**F**) *MMP13* was evaluated in hMSC pellets cultured with/without IL-1β (10 ng/mL) or SS-31 (25 μM) at days 7, 14, 21, and 28 of chondrogenic differentiation. Data are shown as mean ± SD (*n* = 3 biological replicates, CD donors). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

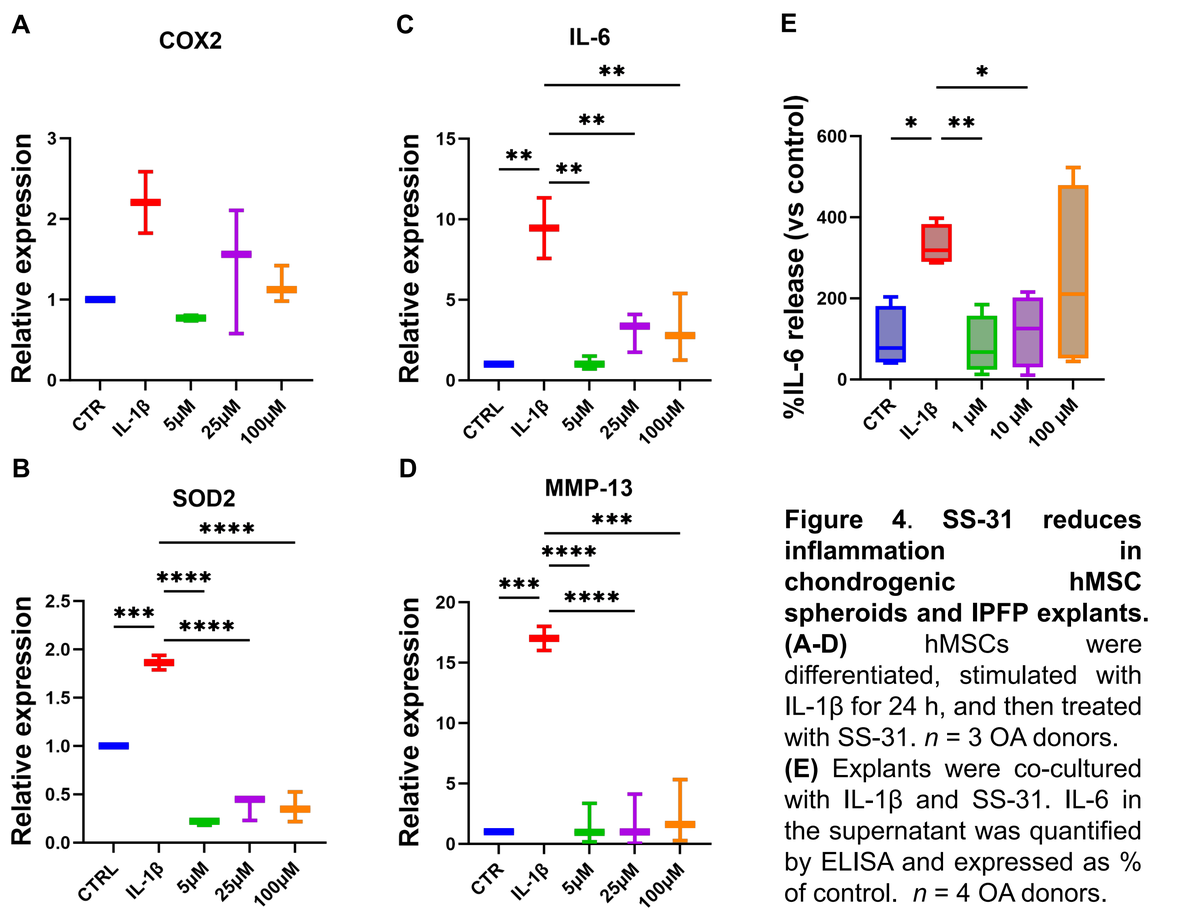


Figure 4. SS-31 reduces inflammation in chondrogenic hMSC spheroids and IPFP explants. (A-D) hMSCs were differentiated, stimulated with IL-1β for 24 h, and then treated with SS-31. *n* = 3 OA donors. **(E)** Explants were co-cultured with IL-1β and SS-31. IL-6 in the supernatant was quantified by ELISA and expressed as % of control. *n* = 4 OA donors.

Conclusion

- Our findings demonstrate that mitochondrial therapy not only enhances chondrogenic differentiation but also counteracts cytokines-induced inflammation, supporting its potential as a therapeutic strategy for OA.

Future work

- Validate SS-31 efficacy in scaffold-based preclinical models of osteoarthritis.
- Develop nanoparticles-assisted delivery strategies to enhance the clinical translation of SS-31 for cartilage regeneration.

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MERLN Institute for Technology-Inspired Regenerative Medicine
provincie Limburg
Maastricht University
Maastricht UMC+