MSC-EVs Modulate Inflammation and Immune Cell Infiltration in Acute Pancreatitis

Sara Shoeibi, Wenyu Gou, Tiffany Yeung, and Hongjun Wang

Department of Surgery, Medical University of South Carolina, Charleston, SC, USA

Background

- **Acute pancreatitis (AP)** is an inflammatory disorder characterized by pancreatic injury and immune cell infiltration, which can often extend to other organs, such as the lungs.
- **The inflammatory cascade** in AP involves the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which drive immune cell infiltration, acinar cell injury, and multiorgan dysfunction.
- **Mesenchymal stem cells (MSCs)** and their secreted products, particularly **extracellular vesicles (EVs)**, are being explored as therapeutic agents for inflammatory diseases.

Objectives

- Investigate the therapeutic effects of bone marrow MSC-derived EVs in a mouse model of cerulein-induced AP.
- Evaluate the ability of MSC-derived EVs to reduce inflammatory cytokine production and ceramide levels.
- Assess the ability of MSC-derived EVs to decrease immune cell infiltration, including neutrophils and macrophages.

Results

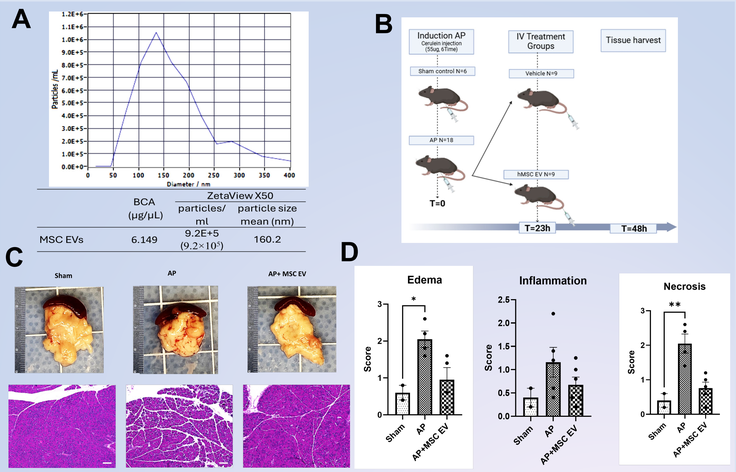

Fig. 1 Reduction of Cerulein-Induced Pancreatitis with Bone Marrow MSC-derived EVs. (A) NTA measured the size distribution of MSC-EVs. **(B)** Overview of the study design and timeline. **(C)** Pancreatic tissues harvested 48 hours post-induction of AP, with H&E staining; scale bar: 100 µm. **(D)** Quantified histopathological scoring of pancreatic tissue. *p < 0.05, **p < 0.01;

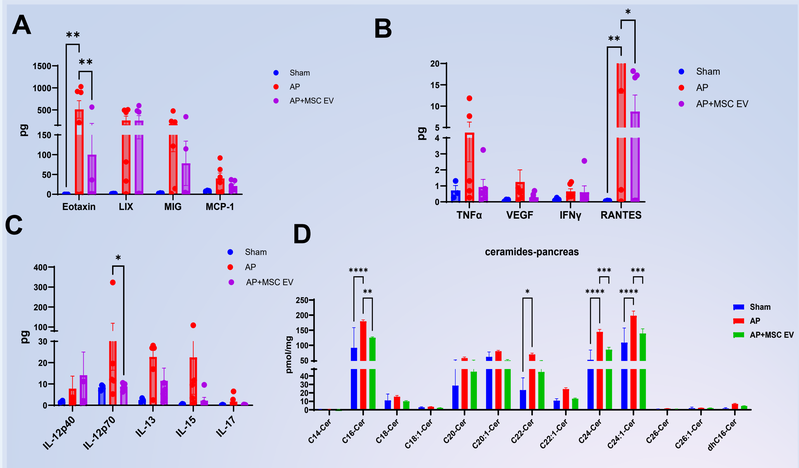

Fig. 2 MSC-derived EVs prevent proinflammatory cytokine production in AP. (A-C) Cytokine levels were measured with cytokine arrays from plasma obtained 48 hours after the first cerulein injection. MSC-EVs significantly reduced the expression of several proinflammatory genes (n = 3–6 per group). **(D)** Ceramide concentrations in the pancreas (n = 3 per group). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001

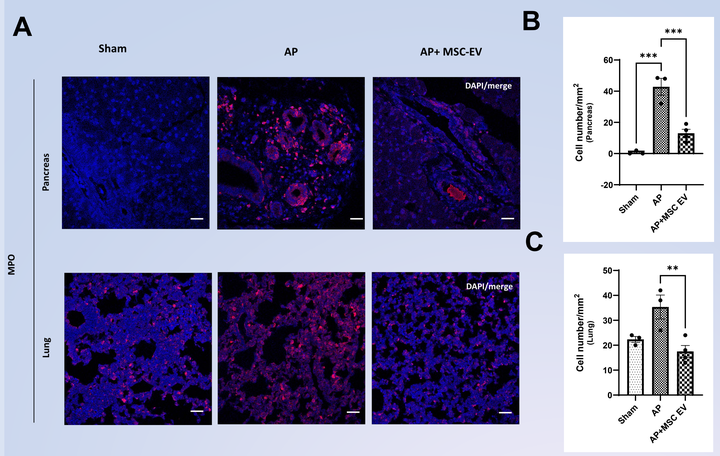

Fig. 4 MSC-derived EVs improve the infiltration of neutrophils and mast cells in AP. (A) Representative immunofluorescence images showing MPO expression in the pancreas and lung; scale bar: 25 µm. Quantifying **(B)** MPO-positive pancreatic acinar and **(C)** lung cells in each group (n = 3–5 per group). **p < 0.01, ***p < 0.001

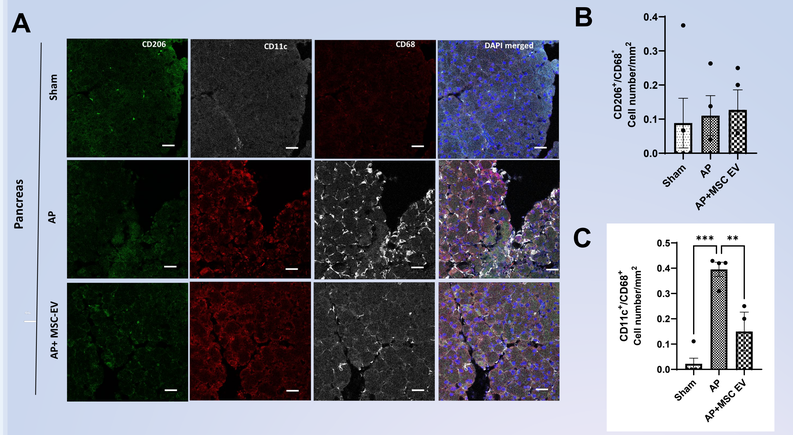

Fig. 3 MSC-derived EVs modulate macrophage polarization in AP. (A) Immunofluorescence staining for CD206, CD11c, and CD68 in the pancreas; scale bar: 25 µm. **(B)** Quantification of CD206/CD68-positive population in the pancreas. AP mice treated with MSC-EVs showed a non-significant increase in the proportion of CD206-positive cells (M2 macrophages) (n = 4 per group). **(C)** Quantification of CD11c/CD68-positive population in the pancreas. AP mice treated with MSC-EVs showed a significant decrease in the proportion of CD11c-positive cells (M1 macrophages) (n = 4 per group). **p < 0.01, ***p < 0.001

Conclusion

Administration of MSC-EVs reduces **cytokine-driven inflammation**, alters **sphingolipid metabolism**, and limits **immune cell infiltration** in a murine model of AP.

Our findings highlight the therapeutic potential of MSC-EVs as a cell-free, scalable, and effective treatment strategy for AP.

References

- Wei H, Chen F, Chen J, Lin H, Wang S, Wang Y, et al. Mesenchymal Stem Cell Derived Exosomes as Nanodrug Carrier of Doxorubicin for Targeted Osteosarcoma Therapy via SDF1-CXCR4 Axis. *Int J Nanomedicine.* 2022;17:3483-95.
- He Z, Hua J, Qian D, Gong J, Lin S, Xu C, et al. Intravenous hMSCs Ameliorate Acute Pancreatitis in Mice via Secretion of Tumor Necrosis Factor-alpha Stimulated Gene/Protein 6. *Sci Rep.* 2016;6:38438.
- Chen G, Xu F, Li J, Lu S. Depletion of neutrophils protects against L-arginine-induced acute pancreatitis in mice. *Cell Physiol Biochem.* 2015;35(6):2111-20.