Piezo1 Regulates Synovial Inflammation and Offers a Therapeutic Target in Arthritis

Donghao Gan[1,2], Francis Y Lee[1], Guozhi Xiao[2]

[1] Department of Orthopaedics and Rehabilitation, Yale School of Medicine, New Haven, CT

[2]Department of Biochemistry, Southern University of Science and Technology, Shenzhen

Email: donghao.gan@yale.edu

Disclosures: Donghao Gan (N), Francis Y Lee (N). Guozhi Xiao[2] (N).

INTRODUCTION: Rheumatoid arthritis (RA) is characterized by chronic synovial inflammation leading to cartilage and bone destruction. Mechanosensitive ion channels such as Piezo1 have been implicated in joint biology, but their role in RA pathogenesis remains poorly defined. We hypothesized that Piezo1 in synovial fibroblasts regulates inflammatory responses and joint damage.

METHODS: We generated *Col1a1-Cre;Piezo1*$^{fl/fl}$ conditional knockout (cKO) mice to delete Piezo1 in synovial fibroblasts and induced arthritis using the collagen antibody-induced arthritis (CAIA) model (6 mice each group, male mice, 6–8 weeks). Synovial tissues from control and cKO mice were analyzed by single-cell RNA sequencing. Cell–cell communication was evaluated using CellChat, and regulon-based transcription factor activity was profiled. Functional studies included construction of a yeast microcapsule (YC)-based oral delivery system for the CXCR4 inhibitor plerixafor (YC-Plerixafor). To test the role of Hif1a, we generated *Col1a1-Cre;Piezo1*$^{fl/fl}$*;Hif1a*$^{fl/fl}$ double knockout (dcKO) mice. In vitro studies were performed using primary synovial fibroblasts under hypoxic conditions. Finally, a synovial-targeted material was engineered to deliver the Piezo1 agonist Yoda1. All animal studies were approved by the institutional animal care and use committee.

RESULTS SECTION: Deletion of Piezo1 in synovial fibroblasts exacerbated CAIA-induced arthritis, with increased synovial inflammation and more severe cartilage and bone destruction ($p<0.01$). Single-cell analysis revealed the expansion of M1 macrophages in cKO joints. Cell cycle analysis indicated these macrophages were not proliferative but recruited via paracrine signaling. CellChat analysis identified CXCL12 (synovial fibroblasts)–CXCR4 (M1 macrophages) as the dominant ligand–receptor axis. Oral YC-Plerixafor significantly reduced synovial inflammation in cKO mice. Regulon-based analysis showed marked upregulation of Hif1a activity in cKO synovium. Double knockout of Piezo1 and Hif1a in synovial fibroblasts reduced arthritis severity compared with Piezo1 single knockout. Mechanistically, Piezo1 loss in synovial fibroblasts under hypoxia increased nuclear Hif1a, pro-inflammatory cytokines, and Mmps expression, while Hif1a deletion abrogated this effect. Targeted delivery of the Piezo1 agonist Yoda1 to synovial fibroblasts reduced synovial inflammation in CAIA mice.

DISCUSSION: Our study identifies Piezo1 as a critical regulator of synovial inflammation in RA. Loss of Piezo1 in synovial fibroblasts activates Hif1a-driven inflammatory pathways and enhances macrophage recruitment through CXCL12–CXCR4 signaling. Targeting these pathways with YC-Plerixafor or Piezo1 agonist-loaded materials reduced arthritis severity in vivo. Limitations include the use of murine models and the need for validation in human RA.

SIGNIFICANCE/CLINICAL RELEVANCE: This work reveals a novel Piezo1–Hif1a axis in synovial fibroblasts that regulates RA pathogenesis and identifies Piezo1 activation and CXCL12–CXCR4 blockade as potential therapeutic strategies to reduce inflammation and joint destruction in RA.