Sirt1–Piezo1 Signaling as a Therapeutic Target for Bone Formation and Fracture Healing

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

INTRODUCTION: Mechanical signaling is essential for bone formation and fracture repair, but the molecular mediators remain incompletely defined. Spatial transcriptomics provides a powerful approach to uncover mechanisms of skeletal repair. Piezo1, a mechanosensitive ion channel, has been implicated in osteogenesis, yet the regulation of its activity during endochondral ossification is not well understood. We hypothesized that Piezo1 activation plays a central role in chondrocyte-mediated ossification and that Sirt1 regulates Piezo1 activity to promote fracture healing.

METHODS: We profiled fracture callus tissues at 4, 7, 14, and 28 days post-fracture using the 10x Genomics Visium platform to map dynamic transcriptional trajectories and pathways involved in endochondral ossification. Conditional chondrocyte-specific Piezo1 knockout mice and pharmacologic Piezo1 activation with Yoda1 were used to assess fracture healing by histology, micro-CT, and biomechanical testing (n=6, male, 12-week-old C57BL/6J mice). Immunoprecipitation, acetylation assays, and pharmacologic activation with SRT2104 or resveratrol (RSV) were used to test Sirt1 regulation of Piezo1. To enhance drug delivery, we developed an oral yeast microcapsule-based RSV formulation (YC-RSV) and an injectable RSV hydrogel (RSV@Gel). All animal studies were approved by the Institutional Animal Care and Use Committee.

RESULTS SECTION: Spatial transcriptomic and histological analyses identified mechanical stress signaling as a key pathway in fracture healing, with Piezo1 expression significantly upregulated in cartilage callus. Loss of Piezo1 in chondrocytes impaired endochondral ossification, delayed fracture healing, and reduced mechanically induced osteogenesis ($p<0.01$). Conversely, Yoda1 activation of Piezo1 enhanced repair. Sirt1 directly bound Piezo1, deacetylated it at K2174, and increased Ca^{2+} influx in chondrocytes. SRT2104 accelerated fracture healing, but its effect was abolished in Piezo1-deficient chondrocytes. RSV also activated Piezo1 and promoted bone repair. YC-RSV showed superior oral bioavailability and fracture-site targeting, while RSV@Gel provided sustained local release, both leading to improved healing outcomes.

DISCUSSION: These findings identify Sirt1 as a novel regulator of Piezo1 in chondrocytes. By deacetylating Piezo1, Sirt1 enhances mechanotransduction, osteogenesis, and fracture repair. Both systemic and local RSV-based therapies demonstrated translational potential. Limitations include reliance on murine models and the need for validation in human fracture healing.

SIGNIFICANCE/CLINICAL RELEVANCE: This study uncovers a Sirt1–Piezo1 regulatory axis in bone repair. Targeting this pathway with Sirt1 activators, including YC-RSV, offers a promising strategy to accelerate bone formation and fracture healing.