PDHA1 Deacetylation by SIRT3 Drives Energetic Metabolism Switching to Enhance Osteoclast Activity in Postmenopausal Osteoporosis

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ABSTRACT INTRODUCTION: Excessive osteoclast-associated bone resorption contributes to pathological bone loss, as observed in senile and postmenopausal osteoporosis. Osteoclast differentiation is accompanied by an increase in mitochondrial DNA (mtDNA) content and oxygen consumption rates, supporting the high energy demand of proton pumping and proteolytic activity during bone resorption. However, how these energy pathways are dynamically coordinated and reprogrammed during osteoclast differentiation remains largely unknown. Pyruvate dehydrogenase E1 subunit alpha (PDHA1), the key catalytic subunit of the pyruvate dehydrogenase complex (PDC), mediates the conversion of pyruvate into acetyl-CoA for entry into the tricarboxylic acid (TCA) cycle, thereby maintaining the balance between glycolysis and oxidative phosphorylation and serving as a central regulator of metabolic reprogramming. SIRT3 has been implicated in regulating osteoclast function by modulating mitochondrial biogenesis and ATP production. However, the detailed mechanism of how SIRT3 regulates osteoclast differentiation through metabolic pathways remain incompletely understood. Emerging evidence indicates that SIRT3 directly deacetylates lysine residues on PDHA1, thereby enhancing its enzymatic activity and shifting cellular metabolism toward oxidative phosphorylation. This study aims to elucidates the role of SIRT3-PDHA1 axis in osteoclast metabolic reprogramming and differentiation.

METHODS: Firstly, bone marrow mononuclear macrophages (BMMs) were isolated from female control and ovariectomized (OVX) mice to detect SIRT3 expression in vivo. Next, SIRT3 was silenced in BMMs from female mice (n = 6), followed by analysis of osteoclast marker genes expression and differentiation. To investigate the *in vivo* role of SIRT3 in osteoclast function and bone homeostasis, we generated osteoclast-specific knockout mice using the Ctsk-cre system. Both male and female mice were used (n = 10 per group). Micro-CT and histological analyses were performed. Metabolic analyses were evaluated via ATP production, mitochondrial membrane potential, oxygen consumption rate and extracellular acidification rate. Metabolite levels of pyruvate, lactate and acetyl-CoA level were measured to assess metabolic flux. Mass spectrometry combined with immunoprecipitation identified the K83 site of PDHA1 as a downstream target of SIRT3. Functional rescue experiments were conducted using wild-type and K83R-mutant PDHA1 in SIRT3-deficient BMMs. Finally, osteoclast-targeted delivery of SIRT3 inhibitor suppresses bone loss in OVX mice. Two-tailed Student's t test, one-way ANOVA and two-way ANOVA tests following post hoc Bonferroni's correction test were used for statistical analysis.

RESULTS SECTION: SIRT3 expression was upregulated in osteoclasts of OVX mice. Cellular study showed that SIRT3 shows the most pronounced induction during osteoclastogenesis. SIRT3 knockdown markedly suppressed osteoclast differentiation and bone resorption in vitro. In vivo study showed that osteoclast-specific SIRT3 cKO mice showed increased bone mass and resistance to OVX-induced bone loss in female mice, while the bone increase phenotype was not observed in male mice. SIRT3 deficiency impaired mitochondrial membrane potential and ATP production, shifting cellular metabolism from oxidative phosphorylation to glycolysis. Mechanistically, SIRT3 deacetylated PDHA1 at lysine 83 to activate PDH complex activity, facilitating pyruvate conversion to acetyl-CoA, maintaining the TCA cycle and oxidative phosphorylation. Furthermore, SIRT3 loss reduced nuclear translocation of PDHA1 and nuclear acetyl-CoA levels, resulting in decreased histone H3K9 and H3K27 acetylation and downregulation of osteoclastogenic genes. Finally, osteoclast-targeted delivery of SIRT3 inhibitor 3-TYP suppresses bone loss in OVX mice via inhibiting osteoclastogenesis and associated bone resorption.

DISCUSSION: In this study, we demonstrated that osteoclast-specific deletion of SIRT3 results in increased bone mass under both physiological and estrogen-deficient conditions, highlighting a critical role of SIRT3 in regulating osteoclast activity. Mechanistically, SIRT3 deficiency disrupted pyruvate metabolism by impairing PDHA1 deacetylation, leading to pyruvate accumulation, reduced acetyl-CoA generation, and a metabolic switch toward glycolysis. These findings suggest that the SIRT3–PDHA1 axis promotes osteoclast differentiation by maintaining aerobic metabolism and acetyl-CoA supply. Beyond its role in energy production, acetyl-CoA may also link metabolism to epigenetic regulation by serving as a substrate for histone acetylation, thereby influencing osteoclast gene expression. This expands our understanding of osteoclast metabolism beyond canonical transcriptional and signaling pathways. Several limitations should be acknowledged. First, although we identified PDHA1 as a downstream target of SIRT3, additional deacetylation substrates may contribute to osteoclast regulation and require further investigation. Second, our study primarily focused on murine models, and whether similar mechanisms apply to human osteoclasts remains to be determined. Third, while metabolic and bone phenotypes were well characterized, the epigenetic consequences of acetyl-CoA reduction were not fully explored. In conclusion, our work identifies SIRT3–PDHA1 signaling as a central metabolic checkpoint in osteoclast function and provides mechanistic insight into how energetic reprogramming contributes to pathological bone resorption.

SIGNIFICANCE/CLINICAL RELEVANCE: This study uncovers a novel SIRT3-PDHA1 axis that promotes osteoclast differentiation by orchestrating a metabolic shift toward oxidative phosphorylation and modulating epigenetic regulation via histone acetylation. Targeting the SIRT3–PDHA1 metabolic axis may represent a potential therapeutic strategy for postmenopausal osteoporosis.

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IMAGES AND TABLES:

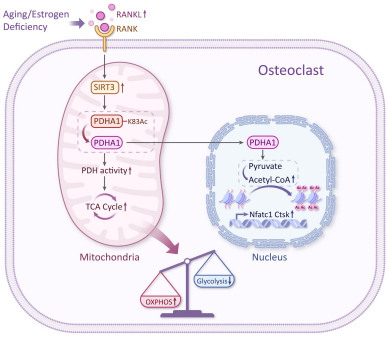

Figure 1. Proposed working model illustrating how SIRT3-mediated deacetylation of PDHA1 regulates osteoclast metabolic reprogramming and contributes to postmenopausal bone loss