

## BAG2-PPAR $\gamma$ -p16-initiated senescence of stem cells promotes bone marrow senescence

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**INTRODUCTION:** Osteoporosis (OP) is acknowledged as a prevalent health concern within the senior population. The intricate mechanisms underlying OP development are not yet fully clear. The current investigation aimed to elucidate the function of BAG2 in bone and BMSCs senescence.

**METHODS:** Serum samples from postmenopausal women with and without OP (OP and non-OP groups, n = 55 and 44, respectively) were collected to quantify BAG2 level. All studies were conducted at the Third Affiliated Hospital of Guangzhou University of Chinese Medicine and approved by the medical ethics committee of the hospital (Approval No. AFSC-12010). 8-week-old BAG2<sup>-/-</sup> female mice and wild-type (WT) female C57BL/6 mice (n=24) were subsequently underwent ovariectomized (OVX). Both WT and BAG2<sup>-/-</sup> mice were subjected to dasatinib (D) plus quercetin (Q) combination intervention (D+Q) to assess whether the intervention could prevent bone damage after BAG2 deletion (n=12). BMSCs were extracted from both BAG2 KO and WT mice. Samples from mice subjected to the following analyses: transcriptome sequencing, immuno-histochemical assay, immunofluorescence assay, calcein green staining, ELISA, tartrate-resistant acid phosphatase staining, reverse transcription-quantitative PCR, Oil Red O staining, alkaline phosphatase staining and Alizarin Red S staining. All animal experiments adhered to the protocols approved by the Animal Care and Use Committee of GZUCM (Approval No. 44002100011060).

**RESULTS SECTION:** A lower serum BAG2 level was noted in the OP patients ( $P < 0.05$ ). Moreover, BAG2<sup>-/-</sup> mice showed downregulated expression of BAG2, which resulted in reduced bone mass ( $P < 0.05$ ). BAG2 KO activated the PPAR $\gamma$ /p16 pathway, which downregulated the expression of osteogenic markers and remarkably promoted cell senescence. Moreover, D+Q intervention could not reverse bone loss in BAG2<sup>-/-</sup> mice. Additionally, BMSCs from the BAG2<sup>-/-</sup> group exhibited damaged mitochondria, indicating that BAG2 KO impaired the function of mitochondria.

**DISCUSSION:** This study provides new insights into the mechanisms underlying bone loss induced by BAG2 knockout. BAG2 is pivotal in controlling several key physiological functions, ranging from maintaining cellular homeostasis and modulating apoptosis to promoting tumorigenesis under pathological conditions. The study initially demonstrated that BAG2 KO negatively affects bone health in both general and OVX model mice. Moreover, D+Q intervention cannot reverse bone loss in BAG2<sup>-/-</sup> mice. The underlying mechanism involves the modulation of PPAR $\gamma$ , which exacerbates BMSC-driven bone aging. Additionally, BAG2 as identified as a crucial modulator of BMSCs and bone formation, thus offering potential therapeutic targets for treating age-related OP. The limitation of the study is the lack of clarity regarding the mechanism of senescence induction by BAG2 KO.

**SIGNIFICANCE/CLINICAL RELEVANCE:** (1-2 sentences): The data presented herein reveal BAG2 as a compelling focal point for the advancement of next-generation therapeutic interventions.

**REFERENCES:** N.

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**IMAGES AND TABLES:**



