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Cellular Senescence in the Bone Marrow Niche Drives Osteoclast-Mediated Bone Resorption in Glucocorticoid-Induced Osteoporosis Through SASP-Derived RANKL

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Abstract

Glucocorticoid-induced osteoporosis (GIOP) is the most common secondary cause of bone loss, yet the cellular senescence contribution remains undefined. We demonstrate that therapeutic-dose dexamethasone induces p16INK4a-positive senescence in bone marrow mesenchymal stromal cells (BMSCs) and osteoblasts within 14 days in murine models. The senescence-associated secretory phenotype (SASP) from these cells exhibited 8-fold elevated soluble RANKL levels compared to non-senescent controls. Senolytic treatment with fisetin or genetic clearance of p16-positive cells abrogated osteoclastogenesis and preserved trabecular bone mineral density despite continued glucocorticoid exposure. Mechanistically, SASP-derived IL-6 amplified RANKL expression through JAK/STAT signaling in pre-osteoclasts. Targeting the senescence-skeletal axis offers a disease-modifying strategy distinct from anti-resorptive bisphosphonates.

Keywords: cellular senescence, glucocorticoid-induced osteoporosis, SASP, RANKL, senolytics, bone marrow niche