Mid-life CDC42 inhibition restores cells of bone remodelling, cytoskeletal architecture and mitochondrial quality to prevent osteoporosis in ageing

Landspersky T.[1,2], Schreck C.[1], Geiger H.[3], Oostendorp R.A.[1], Sacma M.[3]
[1]Technical University of Munich, Klinikum rechts der Isar, Clinic of Internal Medicine III, Munchen, Germany, [2]University Hospital, LMU Munich, Munchen, Germany, [3]Institute of Molecular Medicine, Ulm University, Ulm, Germany

Age-associated osteoporosis is a hallmark of skeletal aging, characterized by trabecular thinning, increased bone resorption, and impaired function of mesenchymal stem and progenitor cells (MSPCs) in the bone marrow niche. Based on our previous findings that CDC42 inhibition mitigates stress-induced bone loss following hematopoietic stem cell transplantation (HSCT), we here investigated whether a short-term pharmacological intervention at mid-life could prevent physiological bone degeneration during aging. Therefore, 10-months-old wild-type mice received a short four-day intervention of the CDC42 inhibitor CASIN and were analyzed one year later at approximately 22-24 months of age. Micro-CT analysis revealed significant preservation of both trabecular and cortical bone thickness in CASIN-treated mice, in contrast to significant osteoporotic changes in untreated age-matched controls. Skeletal remodeling depends on the balance between osteoclast-mediated bone degradation and bone-forming activity of osteoblasts and osteocytes. To assess osteoclast activity during ageing, we measured serum TRAcP 5b levels, a marker of osteoclast number and bone resorption. Aged mice showed elevated TRAcP 5b, while mid-life CASIN treatment restored levels to those of young controls. Histological TRAP staining confirmed reduced osteoclast numbers in CASIN-treated mice. Additionally, CASIN treatment partially restored the number of Osterix+ bonelining cells and increased osteocyte numbers, while also normalizing osteocyte nuclear morphology. Aged mice treated with CASIN preserved MSPC clonogenicity and cytoskeletal integrity, with elongated F-actin fibers in contrast to the disorganized networks seen in aged control mice, which are known to promote osteoporosis (Landspersky et al., Blood Adv. 2024). Colocalization of MYO6 and F-actin indicated restored recognition of damaged mitochondria and preparation for mitophagy, while TOMM20 staining confirmed the preserved mitochondrial architecture and quality control mediated by the cytoskeleton. Overall, our data show that a single, time-limited intervention with a CDC42 inhibitor in middle-aged mice durably preserves bone integrity and niche function during aging by maintaining cytoskeletal organisation and mitophagy and suppressing osteoclast-induced bone loss. These results identify CDC42 as a key regulator of bone ageing and highlight the therapeutic potential of targeting cytoskeletal dynamics to prevent age-related osteoporosis

Landspersky T.1,2, Schreck C.1, Geiger H.3, Oostendorp R.A.1, Sacma M.3
Mid-life CDC42 inhibition restores cells of bone remodelling, cytoskeletal architecture and mitochondrial quality to prevent osteoporosis in ageing (abstract).

Oncol Res Treat 2025;48(suppl 2):13–364