Δ Accelerated Aging Murine Model Exhibits Elevated Systemic Senescence and Delayed Fracture Repair

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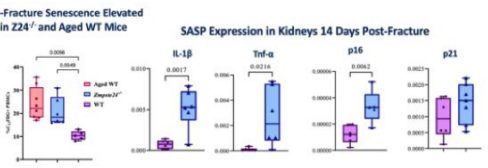
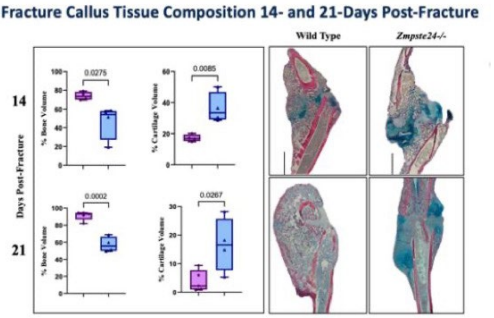
Purpose: Fracture healing is well established to present with significant age-related delays and increased risk for nonunion. The National Institutes of Health standard for studies of age-related pathologies in mice is 24 months of natural aging, a constraint that creates a substantial time and monetary burden for studies that investigate mechanisms or therapies associated with age-related decline in bone healing. The Zmpste24-/-(Z24-/-) mouse model recapitulates premature aged phenotypes of Hutchinson-Gilford progeria syndrome, and this study is the first to leverage the Z24-/- mouse line to model fracture healing in aged mice. We hypothesize that these mice will present with delayed fracture healing compared to age-matched wild-type (WT) controls due to elevated senescent cell burden, chronic inflammation, and reduced fracture healing.

Methods: Age-matched Z24-/- and WT mice (3-4 months), and naturally aged mice (18 months), underwent tibia fracture with intramedullary fixation and were sacrificed 9, 14, and 21 days post-fracture for blood and tissue collection. Blood samples underwent immuno- and senescence phenotyping, and qRT-PCR (quantitative real-time polymerase chain reaction) for senescence associated secretory phenotype (SASP) gene expression in key organs and the fracture callus. Functional healing was quantified from serial tissue sections stained with Hall Brundt's quadruple stain followed by histomorphometry analysis 14 and 21 days after fracture.

Results: Z24-/- mice had significantly elevated levels of systemic senescent compared to young WT mice before and 14 days after fracture and both SASP factors and senescent cell cycle regulators exhibited higher expression in Z24-/- mice 14 days after fracture. qRT-PCR assessment of fracture calli demonstrated dysregulation in bone healing in the Z24-/- mice compared to their WT counterparts, and histomorphometry illustrated that on both 14 and 21 days post fracture, Z24-/- mice had more cartilage and less bone volume within their fracture calli compared to young WT mice.





Conclusion: These findings support that the Z24-/- mouse model recapitulates not only key hallmarks of aging, but more importantly, mimics aberrant fracture repair in naturally aged mice including delayed and incomplete bone formation.

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