Nature Reviews Rheumatology | Published online 14 Sep 2017; doi:10.1038/nrrheum.2017.152

BONE

Targeting old cells to protect old bones

> …treated mice had fewer osteoclasts and less bone resorption than vehicle-treated control mice…

As cells age, they develop a senescent phenotype characterized by the production of pro-inflammatory cytokines that is thought to contribute to several age-related comorbidities. Various cells in the bone microenvironment become senescent over time, but the contribution of these cells to age-related bone loss was unknown. Now, new research shows that removing senescent cells, or blocking their secretory phenotype, results in a reduction in age-related bone loss in mice.

The new study was the result of collaboration between the labs of Sundeep Khosla and James L. Kirkland. "In previous studies, the Kirkland group had demonstrated that clearing senescent cells or inhibiting their inflammatory secretome (the senescence-associated secretory phenotype, SASP) improved cardiovascular function, insulin sensitivity, and frailty in ageing mice," explains Khosla. "Given the importance of osteoporosis as an age-related morbidity, we teamed up to address the question of whether targeting cellular senescence could prevent age-related bone loss in mouse models, with the goal of eventually translating these findings into humans."

To achieve this goal, the researchers used *INK-ATTAC* transgenic mice, which harbour a 'suicide' transgene that enables AP20187-induced selective killing of cells expressing *Cdkn2a* (also known as *P16ink4a*), a gene upregulated in senescent cells. Administration of AP20187 to aged (20–22 months old) *INK-ATTAC* transgenic mice with established bone loss induced the production of caspase 8 in senescent cells, thereby selectively clearing these cells. AP20187-treated mice had fewer osteoclasts and less bone resorption than vehicle-treated control mice, without a concomitant reduction in bone formation. By contrast, treatment of young (12 months old) *INK-ATTAC* transgenic mice with AP20187 had no effect on the measured bone parameters (bone microarchitecture, bone volume fraction and trabecular bone measurements).

The results observed in aged transgenic mice upon AP20187-induced depletion of senescent cells were then replicated in aged C57BL/6 mice by use of two pharmacologic approaches. In the first model, senescent cells were depleted in aged C57BL/6 mice using a combination of the senolytic agents dasatinib (a tyrosine kinase inhibitor) and quercetin (a flavanol). In the second model, components of the SASP (mainly IL-8, IL-6 and plasminogen activator inhibitor-1) were inhibited by administration of the Janus kinase inhibitor ruxolitinib to aged C57BL/6 mice. Both approaches reduced the number of osteoclasts without reducing the number of osteoblasts, thereby ameliorating bone loss, compared with control mice.

"We targeted a fundamental ageing process that has the potential to improve not only bone mass but also to alleviate other age-related conditions as a group," states Kirkland. "Unlike current osteoporosis drugs that inhibit bone resorption and also concomitantly reduce bone formation, targeting senescent cells inhibited bone formation while maintaining or even enhancing bone formation," he continues.

Jennie Vallis/Macmillan Publishers Limited

"Having established 'proof-of-concept' with this study, we are now continuing to identify compounds that eliminate senescent cells or inhibit their secretome," concludes Khosla.

Joanna Collison

ORIGINAL ARTICLE Farr, J. N. *et al.* Targeting cellular senescence prevents age-related bone loss in mice. *Nat. Med.* http://dx.doi.org/10.1038/nm.4385 (2017)