BONE

JAK inhibitors boost bone formation

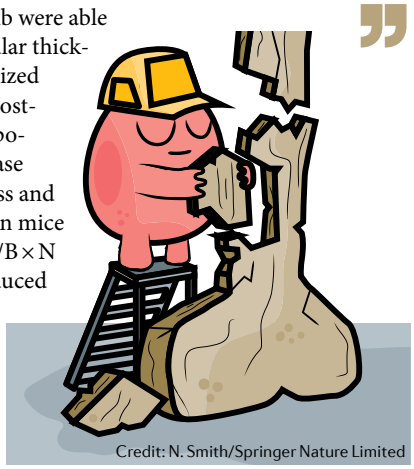
Inhibitors of Janus kinases (JAKs), such as tofacitinib and baricitinib, are used to treat cytokine-mediated inflammatory diseases such as rheumatoid arthritis (RA). Some evidence has emerged to suggest a role for JAK signalling pathways in bone biology, but whether JAK inhibition affects bone remodelling has been uncertain. The results of a new study published in *Science Translational Medicine* shed light on exactly how JAK inhibitors affect bone in health and disease.

"We studied two patients with RA who received 5 mg tofacitinib twice daily," states first author Susanne Adam. "High-resolution peripheral quantitative CT of their metacarpophalangeal joints revealed that tofacitinib treatment reduced bone erosions after 2 years by induction of bone formation."

"Despite the constant progress in anti-rheumatic therapy options, restoring bone tissue that has been subjected to erosive damage by RA has not yet been achieved," explains corresponding author Silke Frey. "Therefore, these findings were unprecedented and encouraged us to investigate the potential bone-anabolic effect of JAK inhibition."

Interestingly, the authors found that 6 weeks of tofacitinib increased bone mass in healthy mice under homeostatic conditions. Both tofacitinib and baricitinib were able to increase trabecular thickness in ovariectomized mice (a model of postmenopausal osteoporosis) and to increase trabecular thickness and cortical thickness in mice with established K/B × N serum transfer-induced arthritis (a model of RA).

> JAK inhibitors reduce bone loss by promoting new bone formation by osteoblasts



Credit: N. Smith/Springer Nature Limited

Delving deeper, the authors discovered that JAK inhibitors reduce bone loss by promoting new bone formation by osteoblasts, rather than by affecting osteoclasts. In vitro experiments and gene network analysis revealed a pathway in which JAK inhibition promotes the stabilization of β-catenin (an important part of the Wnt signalling pathway) and the expression of osteoanabolic genes such as *OCN*, which leads to an increase in the bone mineralization capacity of osteoblasts.

"The capability of JAK inhibitors to directly affect bone metabolism will expand their well-established role as anti-inflammatory agents," says senior author Axel Hueber. "We expect JAK inhibition to not only ameliorate inflammation-induced bone damage, but also to provide additional value in treating osteoporosis-induced loss of bone density, which is a frequent comorbidity of RA."

Joanna Clarke

ORIGINAL ARTICLE Adam, S. et al. JAK inhibition increases bone mass in steady-state conditions and ameliorates pathological bone loss by stimulating osteoblast function. *Sci. Transl Med.* **12**, eaay4447 (2020)

INFLAMMATION

Pro-senescence therapy reduces joint inflammation

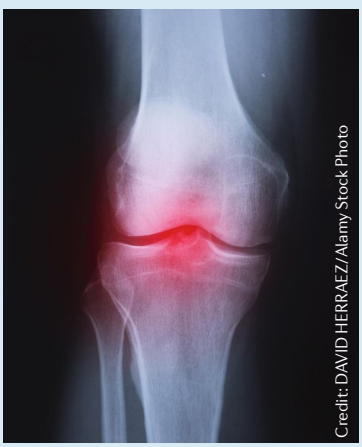
New research shows that inducing senescence of synovial fibroblasts via activation of melanocortin type 1 receptor (MC_1), a G protein-coupled receptor, could offer a novel approach to promote resolution of inflammation in joints affected by rheumatoid arthritis (RA). In the study, administration of a small-molecule MC_1 agonist to synovial fibroblasts from patients with RA not only arrested proliferation of the cells, but also induced a pro-repair phenotype resembling that seen during the remodelling phase of wound healing.

The researchers had previously demonstrated that drugs targeting the pro-resolving melanocortin system had anti-arthritic effects in mouse models of inflammatory arthritis. "In the present work we aimed to translate those findings into human arthritis by studying the effects of melanocortin drugs on human synovial fibroblasts from patients with RA, which are largely responsible for the sustained inflammation and hence lack of resolution within the arthritic joints," explains lead author Trinidad Montero-Melendez.

> BMS-470539 had anti-arthritic effects in association with synovial fibroblast senescence

In the study, treatment of RA synovial fibroblasts with the selective MC_1 agonist BMS-470539, but not with non-selective ligands, induced senescence via phosphorylation of ERK. MC_1 activation modulated processes related to cell cycle regulation, lysosomal function and metabolic processes. BMS-470539-treated cells were also characterized by downregulation of collagens and increased expression of matrix metalloproteinases.

In vivo, in mice with K/B × N serum transfer-induced arthritis, BMS-470539 had anti-arthritic effects in association with synovial fibroblast senescence. Notably, co-administration of senolytic drugs abrogated these anti-arthritic effects.



Credit: DAVID HERRAEZ/Alamy Stock Photo

"Our study shows for the first time that senescence can be induced via the direct activation of a membrane receptor," highlights Montero-Melendez. The results suggest a route to restoring homeostasis to joints affected by RA by directly targeting synovial fibroblasts.

Sarah Onuora

ORIGINAL ARTICLE Montero-Melendez, T. et al. Therapeutic senescence via GPCR activation in synovial fibroblasts facilitates resolution of arthritis. *Nat. Commun.* **11**, 745 (2020)