Nature Reviews Endocrinology **11**, 690 (2015); published online 27 October 2015; doi:10.1038/nrendo.2015.187

BONE

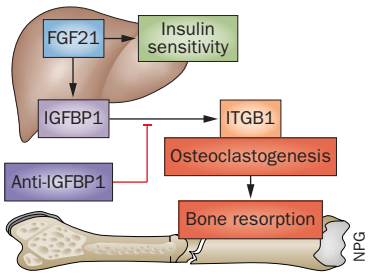
IGFBP1—hepatokine and target for FGF21-mediated bone loss

Insulin-like growth factor-binding protein 1 (IGFBP1) has been identified as a hormone that is produced in the liver and promotes osteoclastogenesis and bone resorption, in a new study published in *Cell Metabolism*. IGFBP1 blockade is now a target for the treatment of conditions such as osteoporosis, and could enable inhibition of bone loss mediated by fibroblast growth factor 21 (FGF21; a potential therapeutic agent for diabetes mellitus), without inhibiting insulin sensitivity.

Wang and co-workers found that mouse liver cells secrete a factor that promotes osteoclast differentiation; this secretion is enhanced by overexpression of FGF21. The liver factor was identified as IGFBP1—osteoclastogenesis was inhibited by an anti-IGFBP1 antibody, and stimulated by murine and human recombinant IGFBP1.

IGFBP1 is highly expressed in the liver, and this expression is responsive to levels of FGF21. *In vivo* administration of IGFBP1 was found to increase bone resorption in wild-type mice. Administration of anti-IGFBP1 antibody to mice overexpressing FGF21 reduced the elevated bone loss seen in these animals to wild-type levels, but did not affect the FGF21-mediated improvement in insulin sensitivity.

Mechanistically, IGFBP1 was found to have no effect on precursor-cell proliferation, but to act via enhancement of osteoclast differentiation. IGFBP1 has a conserved integrin-recognition motif, and is known to bind to integrin β1 (ITGB1). Wang *et al.* generated *Itgb1*-knockout mice and found that they were resistant to the induction of bone resorption by IGFBP1 or FGF21.



These results suggest that "IGFBP1 blockade is an important avenue to prevent the bone-loss adverse effects while preserving the insulin-sensitizing benefits of FGF21 in the treatment of diabetes mellitus," says Yihong Wan, corresponding author of the report. Furthermore, they "highlight an exciting potential for IGFBP1 blockade as a new therapeutic strategy for the treatment of osteoporosis." Ovariectomy—a model for osteoporosis—increased serum levels of IGFBP1 in mice, and the induction of bone loss was abolished by treatment with anti-IGFBP1 antibodies.

Robert Phillips

Original article Wang, X. *et al.* A liver–bone endocrine relay by IGFBP1 promotes osteoclastogenesis and mediates FGF21-induced bone resorption *Cell Metab.* **22**, 1–14 (2015)