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BONE

Regulating osteoclast differentiation to prevent bone loss

Ibrutinib—an orally available anti-cancer drug that inhibits Btk—blocks osteoclast differentiation and function, and suppresses osteoclastic bone resorption, according the results of a new study. "Although it was shown in previous studies that Btk inhibitors may be effective in the treatment of osteoporosis, this study showed that the orally available inhibitor can exert this bone sparing effect well, providing a good possibility of treating osteoporosis with this drug," explains Hiroshi Takayanagi, lead author of the study.

Osteoblasts and osteoclasts are involved in maintaining bone tissue homeostasis. Several bone disorders, including osteoporosis, can result from an imbalance of bone formation and resorption. Ibrutinib has previously been shown to have a beneficial effect on some leukaemias and autoimmune diseases in mice, and has also been shown to have a suppressive effect on osteoclasts *in vitro*. Here, the researchers set out to look at the effects of ibrutinib both *in vitro* and *in vivo* to see if they could develop a strategy for the treatment of osteoclast-associated bone diseases.

> "...ibrutinib regulates the expression of osteoclast-associated genes and suppresses bone destruction..."

The researchers found that NFATc1 (the master transcription factor involved in osteoclast differentiation, and essential for the expression of osteoclast-related genes) is increasingly suppressed with rising doses of ibrutinib in bone marrow-derived macrophages. Furthermore, inhibition of NFATc1, and the subsequent suppression of other osteoclast genes, inhibits osteoclast differentiation. Interestingly, genome-wide screening showed that Btk is involved in regulating the expression of genes involved in osteoclast differentiation and function in an NFATc1-dependent and NFATc1-independent manner. The investigators also used a inducible mouse model of osteoporosis to look at the *in vivo* effects of ibrutinib. 3D microcomputed CT imaging and histological analysis showed that ibrutinib treatment protected against bone loss—bone volume, and trabecular number and thickness, were substantially increased in the treated mice in comparison to control mice.

The results of this study show that ibrutinib regulates the expression of osteoclast-associated genes and suppresses bone destruction, thus highlighting its potential use in the treatment of osteoporosis. "We would now like to investigate the efficacy of ibrutinib in human osteoporosis in collaboration with a pharmaceutical company, and develop a new drug for osteoporosis based on this new molecular mechanism," concludes Takayanagi.

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Original article Shinohara, M. *et al.* The orally available Btk inhibitor ibrutinib (PCI-32765) protects against osteoclast-mediated bone loss. *Bone* doi:10.1016/j.bone.2013.11.025