OSTEOIMMUNOLOGY

Unexpected effects of NFκB in bone formation

It is well known that nuclear factor κB (NFκB) has a crucial role in promoting osteoclast differentiation and bone resorption. Jia Chang and colleagues have now shown that this immune transcription factor also inhibits the function of mature bone-forming osteoblasts. Furthermore, specific inhibition of NFκB increases bone formation and protects against bone loss in an experimental mouse model of osteoporosis.

“NFκB inhibition enhances osteoblast function without affecting osteoclast function”

To study the effects of NFκB in mature osteoblasts, the osteoblast-specific bone γ-carboxyglutamate protein 2 (*Bglap2*) promoter was used to generate transgenic mice specifically expressing inhibitor of

κB kinase (IKK). Histomorphometric analysis at 2 weeks revealed increased trabecular bone mass and a higher rate of bone formation in *Bglap2*-IKK mice compared with their wild-type littermates. Furthermore, numbers of osteoblasts and osteoclasts were similar in both types of mice, as were serum levels of tartrate-resistant acid phosphatase 5b, a marker of bone resorption and osteoclast function. These findings indicate that NFκB inhibition enhances osteoblast function without affecting osteoclast function. The observed increase in Fos-related antigen 1 expression in *Bglap2*-IKK mice could explain these positive effects.

The investigators then sought to determine whether bone formation could be maintained in ovariectomized *Bglap2*-IKK mice. Using micro-CT, they found only 12% loss of bone mineral density in the trabecular bone of *Bglap2*-IKK mice compared with 40% loss

in wild-type animals. They also showed that proinflammatory cytokines, such as tumor necrosis factor and interleukin1, activate NFκB, leading to suppressed osteoblast function and inhibition of bone formation in ovariectomized mice.

The researchers hope that this approach could improve the future treatment of osteoporosis. “At present, many drugs used in the treatment of osteoporosis are bone resorption inhibitors, but they are unable to increase or restore bone mass,” says lead investigator Cun-Yu Wang. “Therefore, identifying a drug that not only inhibits bone resorption but also promotes new bone formation would be a major therapeutic advance.”

Negin Nassabeh

Original article Chang, J. *et al.* Inhibition of osteoblastic bone formation by nuclear factor-κB. *Nat. Med.* **15**, 682–689 (2009).