BONE

Bcl_{XL} blocks bone resorption

The antiapoptotic role of the B cell lymphoma 2 (BCL2) family member BCL_{XL} (also known as BCL2L1) in lymphocytes is well understood, but what role, if any, does this protein have in osteoclasts? A paper published in *The Journal of Clinical Investigation* reports a surprising function for this protein in regulating the bone-resorbing activity, as well as the survival, of these cells.

> "*Bclx* KO osteoclasts had increased bone-resorbing activity and were more susceptible to apoptosis..."

"BCL_{XL} is encoded by the *Bclx* gene," explains Professor Sakea Tanaka from the University of Tokyo, the study's lead researcher. "Since conventional knockout of *Bclx* in mice is embryonic lethal, we generated osteoclast-specific conditional *Bclx* knockout mice, and investigated the survival and function of *Bclx* knockout osteoclasts *in vitro* and bone phenotypes of the mice *in vivo*."

The authors crossed cathepsin-K–Cre transgenic mice (which express Cre recombinase under the control of the osteoclast-specific cathepsin-K promoter) with $Bclx^{fl/fl}$ mice (in which the *Bclx* gene is floxed, which means that in offspring this gene will be spliced out in any cells in which Cre recombinase is expressed) to generate mice in which *Bclx* is knocked out only in osteoclasts (*Bclx* knockout [KO] mice).

The *Bclx* KO mice grew normally, but by 1 year of age trabecular separation was increased and bone mineral density of the distal femur, bone volume per tissue volume, trabecular thickness and trabecular bone number were considerably reduced in these mice in comparison with control $Bclx^{fl/fl}$ mice: the *Bclx* KO mice developed substantial osteopenia. Serum levels of C-terminal cross-linking telopeptide (a marker of bone resorption) were increased in the *Bclx* KO mice compared with the $Bclx^{fl/fl}$ mice, which suggests that the osteopenia resulted from increased bone resorption rather than decreased bone formation. *In vitro* experiments demonstrated that *Bclx* KO osteoclasts had increased bone-resorbing activity and were more susceptible to apoptosis than osteoclasts from $Bclx^{fl/fl}$ mice; overexpression of *Bclx* in these *Bclx* KO osteoclasts by use of adenovirus-mediated transfer rescued this phenotype.

So, how does BCL_{XL} stimulate bone resportion? Tanaka and colleagues carried out further experiments and, as he explains, "We discovered that the increased bone-resorbing function of *Bclx* KO osteoclasts was due to increased activity of c-Src, an essential molecule for bone resorption, which was caused by increased extracellular matrix protein production by *Bclx* KO osteoclasts".

Tanaka concludes that his group plans to extend this research "to further clarify the physiological and pathological role of BCL2 family members in regulating bone homeostasis. For example, it is possible that pathologic bone resorption in osteoporosis and rheumatoid arthritis is regulated by BCL2 family molecules, and, therefore, they could be therapeutic targets for these conditions".

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Original article Iwasawa, M. *et al.* The antiapoptotic protein Bcl-xL negatively regulates the bone-resorbing activity of osteoclasts in mice. *J. Clin. Invest.* **119**, 3149–3159 (2009).