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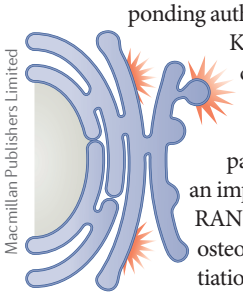
BONE

ER stress causes osteoclastogenesis

> “reducing CREBH expression … caused a reduction in osteoclast differentiation and bone loss in vivo”

Endoplasmic reticulum (ER) stress-activated transcription factor CREBH forms the missing link in receptor activator of NF-κB ligand (RANKL)-induced osteoclastogenesis, according to a new study. Although ER stress proteins had previously been associated with bone-related disorders such as osteoporosis, the mechanisms involved were unclear. New research reveals a distinct signalling pathway that links RANKL, ER stress and CREBH to the expression of transcription factor NFATc1 and osteoclast differentiation.

“We decided to study the role of CREBH in osteoclasts to clarify the effects of ER stress on osteoclast differentiation and the roles of CREBH in bone homeostasis,” explains corresponding author Nacksung Kim. “Our study confirmed that ER stress signalling pathways have an important role in RANKL-induced osteoclast differentiation. A new and important finding is that ER stress regulates osteoclast differentiation through CREBH activation, and that activated CREBH is a transcriptional regulator of NFATc1, which is a master transcription factor for osteoclast differentiation.”



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Kim and colleagues first established that RANKL upregulates genes that act as markers of ER stress during osteoclast differentiation. During ER stress, the cleavage of ER-bound transcription factors, such as CREBH, enables signals to travel to the nucleus. Stimulation of osteoclast precursor cells with RANKL caused an accumulation of activated CREBH in the nucleus, indicating that RANKL-triggered ER stress can initiate a signalling cascade that regulates gene expression.

To determine which genes were regulated by CREBH, the researchers overexpressed activated CREBH in osteoclast precursor cells during differentiation. *Nfatc1* expression was robustly upregulated by activated CREBH, and a putative binding site for activated CREBH in the promoter region of *Nfatc1* was identified, suggesting that CREBH can directly bind to and regulate *Nfatc1* expression in osteoclast precursor cells. In a mouse model of RANKL-induced bone loss, Kim et al. showed that reducing CREBH expression with small interfering RNA caused a reduction in osteoclast differentiation and bone loss in vivo.

Previous studies have highlighted a role for CREBH as a negative regulator of osteoblast differentiation, which, together with these new findings, suggests that targeting CREBH might have a dual effect on the regulation of bone turnover. “Future studies are necessary to clarify the role of CREBH in bone homeostasis under pathological conditions such as rheumatoid arthritis and following ovariectomy,” concludes Kim.

Joanna Collison

ORIGINAL ARTICLE Kim, J. H. et al. Endoplasmic reticulum-bound transcription factor CREBH stimulates RANKL-induced osteoclastogenesis. *J. Immunol.* https://doi.org/10.4049/jimmunol.1701036 (2018)

FURTHER READING Navid, F. & Colbert, R. A. Causes and consequences of endoplasmic reticulum stress in rheumatic disease. *Nat. Rev. Rheumatol.* **13**, 25–40 (2017)