Endoplasmic reticulum (ER) stress is triggered by various metabolic factors, such as cholesterol and proinflammatory cytokines. Recent studies have revealed that ER stress is closely related to skeletal disorders, such as osteoporosis. However, the precise mechanism by which ER stress regulates osteoclast differentiation has not been elucidated. In this study, we identified an ER-bound transcription factor, cAMP response element-binding protein H (CREBH), as a downstream effector of ER stress during RANKL-induced osteoclast differentiation. RANKL induced mild ER stress and the simultaneous accumulation of active nuclear CREBH (CREBH-N) in the nucleus during osteoclastogenesis. Overexpression of CREBH-N in osteoclast precursors enhanced RANKL-induced osteoclast formation through NFATc1 upregulation. Inhibiting ER stress using a specific inhibitor attenuated the expression of osteoclast-related genes and CREBH activation. In addition, inhibition of reactive oxygen species using N-acetylcysteine attenuated ER stress, expression of osteoclast-specific marker genes, and RANKL-induced CREBH activation. Furthermore, inhibition of ER stress and CREBH signaling pathways using an ER stress-specific inhibitor or CREBH small interfering RNAs prevented RANKL-induced bone destruction in vivo. Taken together, our results suggest that reactive oxygen species/ER stress signaling-dependent CREBH activation plays an important role in RANKL-induced osteoclastogenesis. Therefore, inactivation of ER stress and CREBH signaling pathways may represent a new treatment strategy for osteoporosis [1)].

1)

Kim JH, Kim K, Kim I, Seong S, Nam KI, Kim KK, Kim N. Endoplasmic Reticulum-Bound Transcription Factor CREBH Stimulates RANKL-Induced Osteoclastogenesis. J Immunol. 2018 Mar 1;200(5):1661-1670. doi: 10.4049/jimmunol.1701036. Epub 2018 Jan 29. PMID: 29378912.