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INFLAMMATION

Potassium channel regulates osteoclastogenesis

Pathological bone loss in inflammatory arthritis is caused primarily by aberrant activation of osteoclasts. The findings of a new study suggest that the calcium-activated potassium channel KCa3.1 (encoded by *Kcnn4)* is a key mediator of osteoclast differentiation in the presence of pro-inflammatory cytokines, and that directly targeting KCa3.1 could be used to treat bone erosion in this setting.

The research demonstrates that KCa3.1 has a major role in the formation of osteoclasts and in osteoclast-specific gene expression in both inflammatory and non-inflammatory conditions. “Potassium channels have an important role in the regulation of osteoclast differentiation and activity and might be exploited for therapeutic intervention not only for osteoporosis, but also to combat bone loss in inflammatory arthritis,” says the study’s corresponding author, Iannis Adamopoulos.

> “directly targeting KCa3.1 could be used to treat bone erosion in [inflammatory arthritis]”

Microarray analysis showed that KCa3.1 is upregulated in isolated mouse bone marrow macrophages (BMMs) during receptor activator of NF-κB ligand (RANKL)-induced osteoclastogenesis. The expression of KCa3.1 *in vivo* was confirmed by immunofluorescence staining of multinucleated cells at the bone surface of inflamed joints from mice with inflammatory arthritis.

In cultured mouse BMMs stimulated with RANKL and TNF, both genetic deletion of KCa3.1 and use of the specific KCa3.1 inhibitor TRAM-34 led to a decreased number of multinucleated cells compared with wild-type untreated control BMMs. Genetic and pharmacological inhibition of KCa3.1 similarly reduced expression of the osteoclast-specific genes *Mmp9*, *Ctsk* and *Acp5* in BMMs in the presence of RANKL and TNF.

Live cell imaging of cultured BMMs revealed that stimulation with RANKL led to an acute, transient increase in calcium signalling. Inhibiting KCa3.1 by pretreatment with TRAM-34 did not reduce the number of responsive cells or the duration of the RANKL-induced calcium response, but did reduce the amplitude of the response. The researchers also found that KCa3.1 inhibition prevented an increase in phosphorylation of calcium/calmodulin-dependent protein kinase type IV (CaMKIV), a calcium-sensitive enzyme that modulates the activity of the transcription factor cAMP-responsive element-binding protein (CREB) during RANKL-induced osteoclastogenesis.

Further studies showed that KCa3.1 modulates protein expression and activity of NFATc1, the master regulator of osteoclastogenesis, through CREB and proto-oncogene c-Fos. Compared with wild-type control BMMs, *Kcnn4*$^{-/-}$ BMMs showed decreased phosphorylated CREB and reduced expression of *Fos* (a direct transcriptional target of phosphorylated CREB) following stimulation with RANKL or co-stimulation with RANKL and TNF. Genetic deletion of KCa3.1 subsequently led to reduced protein expression and transcriptional activity of NFATc1 in BMMs stimulated with RANKL or with RANKL in combination with TNF.

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