BONE

Cdc42 has a key role in modulating osteoclast formation and function

A new study in mice shows how the small GTPase Cdc42 influences bone modeling and remodeling—it modulates both the formation and function of osteoclasts, and is involved in the downstream signaling pathways of two key cytokines involved in bone resorption, macrophage-colony stimulating factor (M-CSF) and receptor activator of NFκB ligand (RANKL).

The Rho subfamily of small GTPases (including Cdc42) are known to be important regulators of the cytoskeleton, but little is known about how these proteins contribute to bone physiology.

Yuji Ito and colleagues examined the role of Cdc42 by generating and examining two different mouse strains (and their derived primary cells) in which Cdc expression was modified. The researchers showed that loss-of-function mice (in which Cdc42 was absent only in mature osteoclasts) were osteopetrotic and resistant to bone loss, even after removal of the ovaries, which mimics postmenopausal osteoporosis. By contrast,

gain-of-function mice (in which Cdc42 was basally active, owing to deletion of Cdc42Gap, a protein that inactivates Cdc42) were osteoporotic.

In vitro experiments showed that Cdc42 expression in isolated osteoclasts affected levels of bone resorption and that Cdc42 had a prominent role in RANKL and M-CSF signaling pathways—by regulating critical downstream components of these osteoclastogenic signaling molecules and thereby affecting osteoclast proliferation, apoptosis, differentiation and function. The authors conclude that Cdc42 could be a “promising therapeutic target for prevention of pathological bone loss”, especially in postmenopausal osteoporosis.

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