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SPOTLIGHT

Moesin strikes an "Actin"g balance to regulate osteoclast fusion and activity

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Key aspects of osteoclast fusion and its coupling with bone resorption activity are lacking. In this issue, Dufrancias and colleagues (https://doi.org/10.1083/jcb.202409169) shed new light on the mechanism underpinning osteoclast fusion and activity, highlighting the critical role of the ERM family member moesin in this important process.

Bone homeostasis is paramount for skeletal health and is intricately coordinated by the actions of osteoblasts, osteoclasts, and osteocytes. Osteoclasts differentiate from myeloid progenitors in response to RANKL, undergo fusion, and form a specialized bone-resorbing apparatus termed the sealing zone. This bone juxtaposed domain is highly specialized and controlled by extracellular outside-in and inside-out signaling mechanisms that coordinate osteoclast function (1, 2). Specifically, substrate recognition by osteoclasts triggers β3-integrin signaling that leads to assembly and rearrangement of actin filaments to form an actin ring, establishing a tight contact domain between the osteoclast ruffled border and the bone surface. This structure is highly dynamic and is regulated by multiple tyrosine kinase and GTPases, most notably, c-Src kinase, Rho GTPase family kinases, and several other adaptor proteins (2). Among these proteins, ezrin, radixin, and moesin (ERM family) play a major role linking plasma membrane proteins and phospholipids to the cortical actin cytoskeleton to establish and maintain structural and functional properties of various cells, including macrophages and osteoclasts (3, 4). However, the mechanistic details underpinning the ERM proteins' structural and functional role in osteoclasts remain vague.

In a new study, Dufrancais and colleagues (5) provide exciting new insights into the role of moesin in osteoclast fusion and bone-resorbing activity. First, the authors demonstrate that expression and activation of ERMs are increased throughout human and mouse osteoclast differentiation, coinciding with fusion and multinucleation processes. Next, the authors deleted ERM members individually and determined that genetic ablation of moesin, but not ezrin or radixin, accelerated fusion and multinucleation of β3-integrin– and cathepsin-K–expressing osteoclasts, without altering differentiation. These initial observations hinted that moesin is a prominent regulator of cell–cell fusion and multinucleation of osteoclasts.

Mechanistically, force spectroscopy demonstrated elegantly that reduced levels of moesin weakened the attachment of the actin cytoskeleton to the plasma membrane of osteoclasts, facilitating the formation of a greater number of tunneling nanotube (TNT) structures and cell fusion index. This cellular structural change correlated with increased bone resorption by moesin-depleted osteoclasts compared with their wild-type counterparts. TNTs serve as a critical "hotspot" platform that facilitates assembly of proteins at the interface of fusing cells, as evidenced by thickening of TNTs when moesin is depleted. Further, the observation that depletion of moesin decreases membrane to cortical actin attachment suggests that moesin expression and activation limit the dynamic and availability of TNT hotspots, leading to a reduction of osteoclast progenitor fusion. This is a novel concept that warrants further investigation to determine direct targets of moesin.

Interestingly, the effects of moesin on cell fusion and osteoclast activity appear distinct. Specifically, whereas depletion of moesin in mature multinucleated osteoclast no longer affected further fusion, decreased levels of moesin correlate with increased bone resorption. These findings imply that moesin targets specific steps during osteoclast maturation and activity, hence identifying therapeutic targets. This aligns with prior evidence that the cell–cell fusion to generate an osteoclast polykaryon requires formation of membrane structures such as podosomes and "sticky" high-energy protrusions to facilitate hemimembrane fusion of neighboring cells (6, 7). This phenomenon is consistent with the high metabolic activity of osteoclasts, which are rich with mitochondria (8). The finding that moesin regulates cell fusion and activity implies that this protein is likely involved in regulating metabolic and energy metabolism in osteoclasts. The authors further stratified the signaling mechanism by demonstrating that the β3-integrin/RhoA GTPase/SLK pathway regulates phosphorylation and activation of ERM proteins in osteoclasts and that inhibition or depletion of members of this pathway recapitulates the changes in the osteoclast sealing zone and ruffled border observed in moesin-depleted osteoclasts (Fig. 1). Finally, analysis of the bone phenotype of moesin global knockout mice revealed an osteopenic phenotype in 10-wk-old mice resulting from

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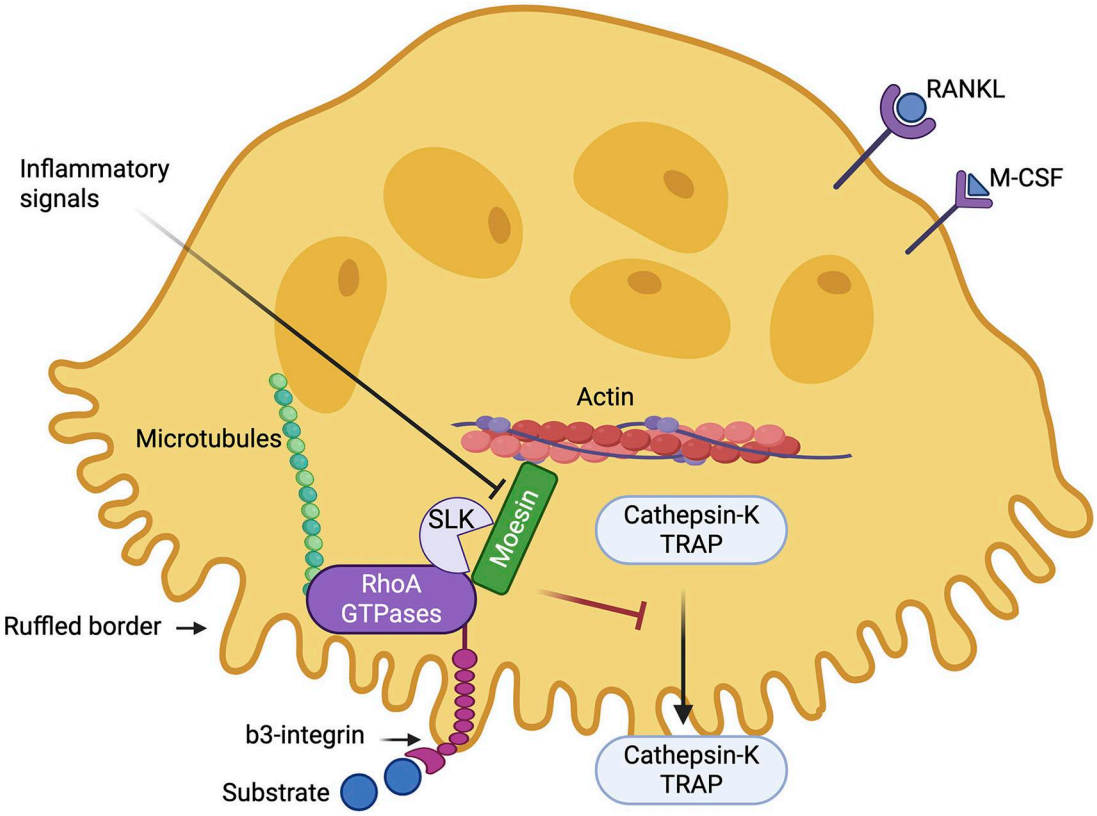

Figure 1. **Regulation of osteoclastogenesis by moesin.** Myeloid progenitors stimulated by RANKL and M-CSF differentiate into β3-integrin–expressing osteoclasts. When these osteoclasts attach to bone, β3-integrin–RhoA–SLK signaling activates moesin. Moesin anchors actin filaments to the plasma membrane, stabilizing the sealing zone and ruffled border needed for controlled bone resorption. Loss of moesin or its inhibition by inflammatory cues weakens this anchorage, promotes TNT formation (not depicted), drives excessive fusion of osteoclasts, and results in increased bone resorption.

lower trabecular volume and number. Osteopenia was further supported by elevated serum levels of C-terminal telopeptide, a bona fide marker of bone resorption, in vivo.

Bone loss is a hallmark of numerous metabolic diseases, arthritis, aging, postmenopause estrogen deficiency, cancer, and a spectrum of chronic inflammatory diseases. Common culprits that mediate bone loss and osteolysis in these disorders include inflammatory cytokines such as TNF, IL-1, IL-6, and other factors that target mature osteoclasts and osteoclast progenitors, inducing both differentiation and activity (9). These cytokines activate major signaling pathways in osteoclasts and their progenitors, such as NF-κB, MAP kinases, and Rho GTPases. The current study demonstrates reduced phospho-ERM levels in HIV-1–infected human osteoclasts, which correlates with a greater fusion index. This observation offers an opportunity to examine the effect of inflammatory cytokines on p-ERMs, especially p-moesin, in disease models of inflammatory bone loss. If indeed expression and/or activity of moesin are reduced under inflammatory conditions, stratifying expression and activity of moesin by genetic or pharmacologic means holds promise to attenuate bone loss. This approach holds notable therapeutic promise, especially in light of the limitations of current treatments. One of the major adverse effects of currently used drugs that induce osteoclast death, such as osteoprotegerin, corticosteroids, and bisphosphonates, is their negative effect on bone remodeling, resulting in weaker bones. Hence, preserving a lower number of osteoclasts in pathologic bone diseases by regulating expression levels of moesin offers a promising breakthrough to inhibit excessive bone loss and maintain healthy remodeled bone.

In conclusion, this study identifies moesin as a primary regulator of osteoclast fusion, multinucleation, and bone-resorbing activity. This finding positions moesin as a strong candidate for the design of a new strategy to strategically and selectively reduce excessive bone loss in various bone pathologies, while preserving basal osteoclast activity essential for bone remodeling, and mitigating the adverse effects of other approaches.

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