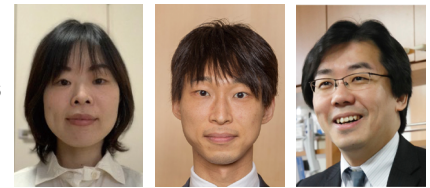


Osteoblast-derived vesicles induce a switch from bone-formation to bone-resorption

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Abstract

Osteoblasts act in a group to make bone over the course of several months. However, how osteoblasts cooperate with each other *in vivo* is still unknown. We established an advanced high-resolution microscopy system to visualize extracellular vesicles secreted and captured by mature osteoblasts *in vivo* and identified a subset of osteoblast-derived vesicles limiting bone formation and stimulating bone-resorbing osteoclast differentiation through a microRNA (miRNA)-mediated mechanism. The osteoblast communication via extracellular vesicles controls the dynamic transition from bone-forming to bone-resorbing phases *in vivo* and could be a target for new treatments for bone diseases.

Background & Results

Bone remodeling occurs in different parts of the body throughout life to maintain bone architecture balance and systemic mineral homeostasis. During this “remodeling” process, osteoclasts remove mineralized bones, whereas osteoblasts form new bones. These resorption and formation phases are linked and balanced with intermittent coupling phases. Functional coupling between these two cell types is critical for the maintenance of proper bone metabolism, and the mechanisms controlling the transition from bone-resorbing to bone-forming phases have been investigated. Nevertheless, the molecular and cellular mechanisms terminating osteoblastic bone formation and promoting osteoclastic bone resorption remain elusive.

Intravital optical imaging using multiphoton microscopy can help dissect *in vivo* cellular dynamics in various intact tissues and organs. To understand the spatiotemporal dynamics of bone remodeling *in vivo*, we have established an intravital imaging technique to visualize the intact bone tissues of living mice. Using this method, we explored the interplay between bone-destroying osteoclasts and bone-forming osteoblasts. However, the spatial resolution of intravital bone imaging was insufficient to visualize structures smaller than cells.

We established an advanced high-resolution microscopy system to visualize extracellular vesicles secreted and captured by mature osteoblasts *in vivo* and identified a subset of osteoblast-derived vesicles limiting bone formation and stimulating osteoclast differentiation, thus regulating the switch from bone formation to bone resorption through a microRNA (miRNA)-mediated mechanism.

Significance of the research and Future perspective

What determines to switch bone formation to resorption has still been unclear. We showed intercellular communication via extracel-

lular vesicles from bone-making osteoblasts is a key factor for the switching through a microRNA-mediated mechanism. The osteoblast communication via extracellular vesicles controls the dynamic transition from bone-forming to bone-resorbing phases *in vivo* and could be a target for new treatments for bone diseases.

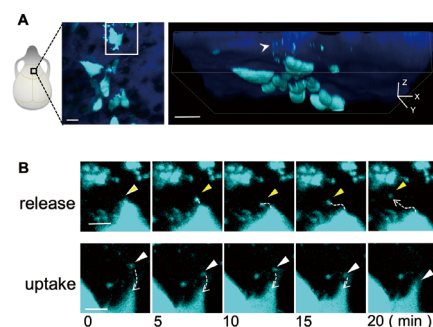


Fig. 1 A, Schematic showing intravital imaging analysis of skull bone of mice. Cyan shows osteoblasts and their extracellular vesicles; blue shows bone tissue. B, Representative consecutive images of osteoblast vesicles released and captured by osteoblasts.

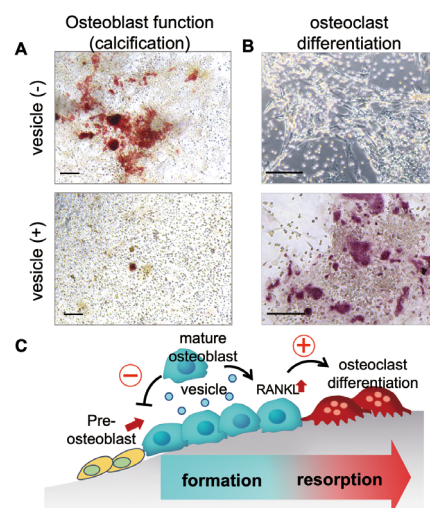


Fig. 2 A, Representative images of Alizarin Red S staining showing calcification of osteoblasts treated with or without vesicles. Red: calcification. Scale bar: 200 μm . B, Representative image of mature osteoclasts among osteoclast precursors co-cultured with vesicle-treated osteoblasts or control osteoblasts. Red: mature osteoclast. Scale bar: 100 μm . C, Interactions among mOBs via SOVs inhibit osteoblastic bone formation and stimulate osteoclast formation, thus switching from the bone formation phase to the bone resorption phase.

Patent

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URL

Keyword

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bone metabolism, intravital imaging, extracellular vesicle, osteoblast, osteoclast