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Perspective

Regulation of Bone Remodeling by Osteocyte-Derived RANKL in Response to Mechanical Unloading

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DESCRIPTION

Mechanical loading represents a fundamental stimulus for bone maintenance, with mechanical unloading leading to rapid bone loss through increased bone resorption and decreased bone formation. Osteocytes, the most abundant bone cells, function as mechanosensory cells that detect mechanical stimuli and regulate bone remodeling responses. Recent evidence suggests that osteocyte-derived Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) plays key roles in mediating bone loss during mechanical unloading. This investigation examined the mechanisms through which osteocytes regulate bone remodeling in response to mechanical unloading.

Bone remodeling is a dynamic and tightly regulated process that maintains skeletal integrity by balancing bone resorption and formation. This process is primarily orchestrated by the coordinated actions of osteoclasts (bone-resorbing cells) and osteoblasts (bone-forming cells), under the regulation of osteocytes-the most abundant and long-lived cells embedded within the bone matrix. Among the key molecular mediators of this balance is Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), a cytokine essential for osteoclast differentiation and activation. Emerging evidence highlights the critical role of osteocyte-derived RANKL in sensing mechanical stimuli and regulating bone remodeling, particularly under conditions of mechanical unloading such as prolonged bed rest, microgravity, or immobilization.

Mechanical loading is known to maintain bone mass by stimulating osteocyte activity and promoting anabolic signaling. In contrast, mechanical unloading leads to reduced skeletal stimulation and disrupts normal remodeling dynamics. Under unloading conditions, osteocytes alter their gene expression profile, notably upregulating RANKL and downregulating its decoy receptor, Osteoprotegerin (OPG). This shift enhances the RANKL/OPG ratio, thereby increasing osteoclastogenesis and bone resorption. Osteocyte-derived RANKL acts in a paracrine manner, binding to its receptor RANK on pre-osteoclasts and triggering their maturation into bone-resorbing osteoclasts. This mechanism explains the significant bone loss observed during disuse or reduced mechanical strain.

Animal models and genetic studies have confirmed the indispensability of osteocyte-specific RANKL in mediating bone loss due to unloading. Mice with conditional deletion of RANKL in osteocytes exhibit resistance to bone loss when subjected to tail suspension or hindlimb unloading, highlighting the pivotal role of this signaling axis. Furthermore, osteocytes respond to unloading by altering their lacuno-canalicular network and mechanosensitive ion channels, which likely influence RANKL expression through downstream pathways involving sclerostin, prostaglandins, and Wnt signaling modulators.

Therapeutic targeting of RANKL has been explored in clinical settings using monoclonal antibodies such as denosumab, which mimics the action of OPG by neutralizing RANKL activity. While effective in treating osteoporosis and cancer-related bone disease, systemic inhibition of RANKL can impair normal bone remodeling. Therefore, a deeper understanding of the regulatory mechanisms governing osteocyte-specific RANKL expression, especially in response to mechanical unloading, may lead to more selective and safer therapeutic strategies.

In summary, osteocyte-derived RANKL is a central mediator of bone resorption in mechanically unloaded bone. By translating mechanical cues into biochemical signals, osteocytes adjust RANKL production to modulate osteoclast activity in response to changes in skeletal load. This adaptive mechanism ensures bone remodeling remains responsive to mechanical demand but also becomes detrimental during prolonged disuse. Ongoing research into the molecular pathways linking mechanical sensing to RANKL regulation may offer novel insights for combating disuse-induced osteoporosis and other skeletal disorders associated with reduced mechanical loading.

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