



# OSTEOCLAST

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## Abstract

Osteoclasts are the primary bone-resorbing cells that play a crucial role in skeletal development, adult bone remodeling, and the pathogenesis of various bone disorders.

In summary, this abstract emphasizes the crucial role of osteoclasts in regulating the balance between bone resorption and formation.

## **Introduction**

Osteoclasts, the sole cells that are capable of resorbing bone, and are crucial for maintaining bone homeostasis and contribute to bone damage in conditions such as osteoporosis, arthritis, periodontitis, and bone metastasis.<sup>1</sup> Osteoclasts are responsible for degrading bone to initiate normal bone remodeling and, under pathological conditions, mediate bone loss by enhancing their resorptive activity.<sup>2</sup> Recent single-cell technology studies have revealed that regulatory mechanisms behind osteoclastogenesis with remarkable detailing, suggesting potential heterogeneity in the origin, function, and fate of osteoclast lineage cells.<sup>3</sup>

## **Origin of Osteoclasts-Osteoclastogenesis**

Osteoclastogenesis is the biological process which is responsible for the formation of osteoclasts. This process is essential for maintaining bone health, as osteoclasts play a key role in bone remodeling by breaking down old or damaged bone tissue.<sup>4</sup>

The origin of osteoclasts revolves around two main theories:

- Multipotential osteoprogenitor cell theory
- Hematopoietic stem cell theory.<sup>5</sup>

Early studies suggested that osteoclasts might originate from this precursor cell within the periosteum or through the fusion of preexisting osteoblasts.<sup>6</sup>

According to hematopoietic theory, osteoclasts are derived from cells within the monocyte-macrophage lineage. Baron and colleagues, using an in vivo model of osteoclast formation, showed that the mononuclear cells that first adhere to the bone surface contain nonspecific esterase. As these cells differentiate, they begin to express tartrate-resistant acid phosphatase (TRAP), a marker enzyme characteristic of osteoclasts. Over time, these cells lose their nonspecific esterase activity and fuse to form multinucleated osteoclasts.<sup>7</sup>

Key regulators in osteoclastogenesis

- RANKL
- M-CSF
- Osteoprotegerin
- Hormones (eg: parathyroid, Vitamin D) • Transforming growth factor beta
- Nitric oxide
- Prostaglandins

<sup>4</sup> Roodman, "Cell Biology of the Osteoclast."

<sup>5</sup> Kurihara et al., "Identification of Committed Mononuclear Precursors for Osteoclast-Like Cells Formed in Long Term Human Marrow Cultures\*."

<sup>6</sup> Yahara et al., "The Origins and Roles of Osteoclasts in Bone Development, Homeostasis and Repair."

<sup>7</sup> Roodman, "Cell Biology of the Osteoclast."

## •Calcitonin<sup>8</sup>

•Macrophage Colony-Stimulating Factor (M-CSF)M-CSF plays an essential role in survival, proliferation, and differentiation of osteoclast precursors. It binds to specific receptors on the surface of these precursors, aiding in their maturation into osteoclasts.<sup>9</sup>

•RANKL:RANKL (Receptor Activator of Nuclear Factor )Kappa is a crucial signaling molecule that binds to its receptor, RANK, located on osteoclast precursors.<sup>10</sup>

•Transforming growth factor beta (TGF- $\beta$ ) :is considered a crucial factor in linking bone formation to prior bone resorption.<sup>10</sup>

•OPG:Osteoprotegerin (OPG) serves as a decoy receptor that binds to RANKL, preventing it from interacting with RANK. By inhibiting the RANKL-RANK binding, OPG naturally regulates osteoclastogenesis, helping to maintain a balance between bone resorption and formation.<sup>11</sup>

Nitric oxide: Nitric oxide is a powerful signaling molecule with diverse functions across bone.<sup>12</sup> Calcitonin:a peptide hormone produced by the parafollicular cells of the thyroid gland, is a powerful inhibitor of osteoclastic bone resorption.<sup>13</sup>

## Morphology of Osteoclasts

The osteoclast is a large, multinucleated giant cell that typically contains 10-20 nuclei per cell, with a range of 2-100 nuclei. It differs from macrophage polykaryons in size and structure.<sup>14</sup> Osteoclasts can reach up to 100  $\mu\text{m}$  in diameter and are usually found on endosteal surfaces within the Haversian system and on the periosteal surface beneath the periosteum Phenotypic Character of Osteoclasts Marker enzymes for osteoclasts

Osteoclasts exhibit unique phenotypic features beyond their distinct morphology, including high levels of acid hydrolases like tartrate-resistant acid phosphatase (TRAP). Immunohistochemical studies have detected TRAP in:

<sup>8</sup> Matsuzaki et al., "Osteoclast Differentiation Factor (ODF) Induces Osteoclast-like Cell Formation in Human Peripheral Blood Mononuclear Cell Cultures."

<sup>9</sup> Xu et al., "The Effect of Cytokines on Osteoblasts and Osteoclasts in Bone Remodeling in Osteoporosis."

<sup>10</sup> Xu et al.

<sup>11</sup> Xu et al.

<sup>12</sup> Xu et al.

<sup>13</sup> Xu et al. <sup>15</sup> b

- Lysosomes
- Golgi apparatus
- Extracellular channels of the ruffled border
- The space between cells and bone<sup>14</sup>

The TRAP has been used for targeted gene expression in osteoclasts in transgenic mice.<sup>15</sup>

Despite its unclear physiological function, studies suggest TRAP plays a role in osteoclastic bone resorption. However, recent knockout mouse models have revealed that TRAP is not primarily involved in bone resorption but rather in endochondral bone formation. TRAP's exact functions remain to be determined.<sup>16</sup>

#### Surface phenotype of the osteoclast

Athanasou and colleagues have extensively characterized the surface phenotype of osteoclasts, showing that human, rabbit, and avian osteoclasts react with monoclonal antibodies against human  $\beta$ -integrins. Additionally, they found that tartrate-resistant acid phosphatase (TRAP) is present in various cellular compartments, including lysosomes, Golgi, extracellular channels of

the ruffled border, and the space between cells and bone.<sup>17</sup>

Initially, TRAP was thought to be exclusive to osteoclasts and a few other cell types. However, recent RT-PCR studies have revealed TRAP expression in multiple tissues, including the gut, kidney, and lung. Bone tissue exhibits the highest levels of TRAP, making it a suitable marker enzyme for osteoclasts.<sup>18</sup>

<sup>14</sup> Reddy et al., "Characterization of the Mouse Tartrate-Resistant Acid Phosphatase (Trap) Gene Promoter."

<sup>15</sup> Reddy et al., "Characterization of the 5'-Flanking Region of the Human Tartrate-Resistant Acid Phosphatase (TRAP) Gene."

<sup>16</sup> Reddy et al.

<sup>17</sup> "Athanasou NA, Alvarez JI, Ross FP, Quinn JM, Teitelbaum SL 1992 Species Differences in the Immunophenotype of Osteoclasts and Mononuclear Phagocytes. *Calcif Tissue Int* 50:427-432."

<sup>18</sup> "Athanasou NA, Alvarez JI, Ross FP, Quinn JM, Teitelbaum SL 1992 Species Differences in the Immunophenotype of Osteoclasts and Mononuclear Phagocytes. *Calcif Tissue Int* 50:427-432."

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Horton and colleagues developed monoclonal antibodies that target osteoclasts, using osteoclastoma tissue from human giant cell tumors of bone as the immunogen. They created several antibodies, including 23c6 and 13c2, which bind to the osteoclast vitronectin receptor, a member of the integrin family. Initially, the 23c6 antibody was thought to be specific to osteoclasts, but

subsequent studies revealed that macrophages and macrophage polykaryons also express the vitronectin receptor.<sup>20</sup>

Kukita and colleagues developed another monoclonal antibody, Kn22, which targets osteoclasts and osteoclast precursors. This antibody can also bind to early macrophage lineage cells and enrich osteoclast precursors.<sup>21</sup> These findings demonstrate the utility of monoclonal antibody techniques in identifying antigens preferentially expressed on osteoclasts.<sup>22</sup>

### Calcitonin Receptor

The calcitonin receptor is a promising differentiation marker for osteoclasts. Recent studies have cloned the calcitonin receptor from several species, revealing at least two isoforms. One isoform, CIA, is predominantly expressed in osteoclasts.<sup>23</sup>

Research by Ikegame et al. and Goldring et al. has examined the expression of calcitonin receptor isoforms in osteoclasts and giant cells from human osteoclastomas.<sup>24</sup>

Takahashi et al. demonstrated that calcitonin receptor expression occurs late during osteoclast precursor differentiation, when cells are committed to the osteoclast lineage and are postmitotic.<sup>25</sup>

### PTH Receptor

<sup>19</sup> Roodman, "Advances in Bone Biology: The Osteoclast."

<sup>20</sup> Roodman.

<sup>21</sup> Roodman.

<sup>22</sup> Roodman.

<sup>23</sup> Goldring et al., "Characterization of the Structural and Functional Properties of Cloned Calcitonin Receptor cDNAs."

<sup>24</sup> Goldring et al.

<sup>25</sup> Pondel, "Calcitonin and Calcitonin Receptors."

Recent studies have challenged the longheld belief that osteoclasts do not express parathyroid hormone (PTH) receptors. Agarwala and Gay, as well as Teti et al., have reported that osteoclasts from mice and birds express PTH receptors.<sup>26</sup>

However, the significance of this expression in mature osteoclasts remains unclear, as highly purified mature osteoclasts do not respond to PTH.<sup>27</sup>

Earlier research by Hakeda et al. used immunocytochemical techniques to show that osteoclast precursors derived from murine hematopoietic blast cells express PTH receptors. This suggests that PTH may directly act on osteoclast precursors to induce their differentiation.<sup>28</sup>

**Functions** Osteoclasts are essential cells in bone remodeling, crucial for maintaining bone health. Their primary roles include breaking down bone tissue to release minerals into the bloodstream, working with osteoblasts to balance bone formation and resorption, regulating blood calcium levels, and aiding in bone repair by clearing damaged tissue. Their activity is tightly controlled by hormones like parathyroid hormone (PTH) and calcitonin to ensure proper bone health.<sup>29</sup>

### Osteoclast Differentiation and Activity

Osteoclast differentiation is marked by several key features, including the fusion of mononuclear osteoclasts to form multinucleated cells. This fusion expands the cell's surface area, enabling it to resorb larger sections of bone. The cells synthesize a vacuolar proton pump and secrete acids that dissolve the bone mineral. They also develop ruffled borders for efficient acid secretion and create a sealing zone to prevent leakage, ensuring that the bone resorption process is tightly controlled<sup>30</sup>

### Coordination with Osteoblasts in Bone Remodeling

An imbalance in the activity of these cells can lead to bone disorders. For example, insufficient osteoclast activity, such as in osteoclastogenesis defects, can result in

<sup>26</sup> Agarwala and Gay, "Specific Binding of Parathyroid Hormone to Living Osteoclasts."

<sup>27</sup> Agarwala and Gay.

<sup>28</sup> Mannstadt, Jüppner, and Gardella, "Receptors for PTH and PTHrP."

<sup>29</sup> Miyamoto, "Regulators of Osteoclast Differentiation and Cell-Cell Fusion."<sup>30</sup> Miyamoto.

osteopetrosis, characterized by overly dense bones. Conversely, excessive osteoclast activity or a relative decrease in bone formation by osteoblasts can lead to conditions like osteoporosis, where bone mass is reduced.<sup>30</sup>

### Ca<sup>2+</sup> Mobilization in Osteoclasts

Calcium ions (Ca<sup>2+</sup>) function as a crucial second messenger in osteoclasts, regulating various signaling pathways essential for bone resorption. Different stimuli influence Ca<sup>2+</sup> concentrations within osteoclasts, affecting their activity and attachment to the bone matrix.<sup>31</sup>

Extracellular acidification has been shown to decrease intracellular Ca<sup>2+</sup> levels in chicken osteoclasts, which enhances their adhesion to bone.<sup>32</sup>

Osteoclasts express  $\alpha v \beta 3$  integrin receptors, which are vital for their function and adhesion to the bone matrix. Activation of these receptors can cause a transient Ca<sup>2+</sup> response, even in the absence of extracellular Ca<sup>2+</sup>.<sup>33</sup>

### Integrin-Dependent Signal Transduction in Osteoclasts

In osteoclasts, integrin ligands, including RGD-containing peptides and proteins, initiate several signaling-related changes.

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These changes include alterations in intracellular calcium levels, protein tyrosine phosphorylation, and cytoskeletal reorganization.<sup>34</sup>

### Conclusion

**Osteoclasts: Regulators of Bone Resorption.** Osteoclasts, the primary cells responsible for bone resorption, have been found to be secretory cells capable of producing both stimulators and inhibitors of their own formation and activity. This discovery has provided valuable insights into the regulation of normal osteoclast function.

The identification of the roles played by proto-oncogenes, such as c-fos and pp60csrc, in osteoclast differentiation and bone resorption has been particularly important.

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<sup>30</sup> Miyamoto and Suda.

<sup>31</sup> Miyamoto, "Regulators of Osteoclast Differentiation and Cell-Cell Fusion."

<sup>32</sup> Miyamoto.

<sup>33</sup> Miyamoto.

<sup>34</sup> Miyamoto.

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