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Author : Ayu Melisa, and Aini Hariyani Nasution
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Osteoclast In Alveolar Bone: Maintaining Bone Homeostasis

Ayu Melisa[1], Aini Hariyani Nasution[2]

[1] *Periodontic Residency Program, Faculty of Dentistry, Universitas Sumatera Utara, Medan, Indonesia*
[2]*Department of Periodontics, Faculty of Dentistry, Universitas Sumatera Utara, Medan, Indonesia*

aini@usu.ac.id

Abstract

The alveolar bone, containing hematopoietic and mesenchymal stem cells, supports tooth roots and is crucial for supporting teeth and surrounding soft tissues. The balance of osteoblasts causing bone formation and osteoclasts causing bone resorption is essential in maintaining bone homeostasis. Osteoclasts, bone cells responsible for bone remodeling and resorption of old bone, are vital to the process. Osteoclasts, derived from immature monocytic cells, monocyte-derived dendritic cells, and macrophages, are crucial in bone resorption, an essential process in bone remodeling and maintenance. Bone homeostasis depends on the balance between osteoclasts, osteoblasts, their precursors, and immune regulators. The interaction between osteoblasts and osteoclasts will manage bone remodeling. The bone remodeling cyclic process involves four stages: activation, resorption, reversal, and formation. Additionally, this review will discuss the association between osteoclasts and periodontitis. Osteoclasts play a significant part in bone remodeling and maintaining bone homeostasis. It also explores the correlation between osteoclasts and periodontitis, understanding the importance of osteoclast biology for effective treatments.

Keywords: Osteoclast; bone homeostasis; bone remodeling; bone resorption; periodontitis

1. Introduction

The alveolar bone is a supporting and enclosing structure that surrounds and supports the tooth roots of the lower jaw. It also provides support for surrounding soft tissue. The alveolar bone is a reservoir of hematopoietic and mesenchymal cells. The bone can be remodeled through the activity of mesenchymal osteoblasts and hematopoietic osteoclasts [1]. Alveolar bone defects that cannot be repaired by themselves will cause damage to the jawbone and periodontal tissues, leading to tooth loss, oral and jaw dysfunction, and affecting aesthetic appearance [2].

The precursors of hematopoietic stem cells (HSCs) involved in bone resorption are osteoclasts, which are multinucleated cells. The balance of osteoblasts causing bone formation and osteoclasts causing bone resorption is essential to maintaining bone homeostasis. Osteoclasts, the bone cells that manage bone remodeling and resorption of old bone, play a vital part for this process. Furthermore, osteoclasts are essential for forming, preserving, and restoring dental tissue through bone resorption. Excessive levels of osteoclast activity have been associated with oral bone diseases, including periodontitis [3]

Reviewing the role of osteoclasts in maintaining bone homeostasis in the alveolar bone provides insights into both the physiological mechanisms of bone remodeling and the clinical implications for dental and skeletal health. This process is particularly crucial in the alveolar bone, which supports the teeth because it allows the bone to adapt to mechanical stresses and maintain its structural integrity.

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2. Alveolar Bone

Intramembranous and endochondral ossification are the two distinct ossification processes that result in the formation of bones. A biological process known as intramembranous ossification produces bone matrix by directly differentiating mesenchymal cells into osteoblasts. Endochondral ossification is a mechanism that happens when mesenchymal cells aggregate and develop into cartilage primordia. Later in development, bones replace tissue made of cartilage [4, 5]

Alveolar bone in the jaws is formed by intramembranous and endochondral ossification and originates from the dental mesenchyme, which consists of dental follicles surrounding the developing tooth seed. During tooth formation, the dental papillae produce odontoblasts and dental pulp. The dental follicle is responsible for producing periodontal ligament, or PDL. It also produces cementum and alveolar bones. The alveolar bone comprises two primary elements: the primary and supporting alveolar bone. The significant role of the alveolar bone is to offer support for the tooth root and uniformly distribute occlusal force [3, 6]

3. Hematopoietic Stem Cell Precursors and Osteoclastogenesis

Hematopoietic stem cells (HSCs) produce osteoclasts, large multinucleated cells specialized for bone resorption. HSCs undergo differentiation into multipotent progenitors (MPPs), leading to lineage-restricted precursors. These precursors subsequently differentiate into common myeloid progenitors (CMPs) and common lymphoid progenitors (CLPs). CMPs further differentiate into megakaryocyte/erythrocyte progenitors (MEPs) and are stimulated by granulocytes or macrophage-stimulating factor (GM-CSF) to differentiate into granulocyte/macrophage progenitors (GMPs). GMPs then differentiate into a common macrophage/osteoclast/dendritic cell progenitor (MODP), with dendritic cells (DCs) serving as an antigen-presenting cell (APC) population crucial for the adaptive immune system. GMPs subsequently differ into osteoclast progenitors and monocyte or macrophage lineages. The osteoclast progenitors subsequently enter the bloodstream, fuse, and ascend to the surface [3, 7]

Chemokines such as CCL2, CXCL16, and CX3CL1 attract immature osteoclasts to areas of inflammation, stimulating their growth and development. Additionally, osteoclasts secrete chemokines to facilitate osteoclastogenesis and bone resorption [8] Osteoclastogenesis mainly depends on the M-CSF and RANKL. M-CSF, often referred to as CSF-1, is created by different kinds of cells, such as osteoblasts, bone lining cells, adipogenic mesenchymal stromal cells, and microvascular endothelial cells. It stimulates monocyte cell differentiation into osteoclast precursors, influenced by RANKL (Receptor Activator of Nuclear Factor κB Ligand) [3, 9] RANKL, also referred to as TRANCE (TNF-related activation-induced cytokine), ODF (osteoclast differentiation factor), or OPGL (osteoprotegerin ligand), is generated by osteoblasts, osteogenic stromal cells, lining cells, and proliferative chondrocytes [10] Derived from osteocytes, RANKL binds to RANK, activating transcription factors such as c-Fos and NFATc1 (nuclear factor of activated T cells, cytoplasmic 1), along with MAPK and NF-kβ signaling pathways. This activation influences osteoclast-specific genes like tartrate-resistant acid phosphatase (TRAP) and cathepsin K [3–5, 7–12].

Prostaglandins and other cytokines such as TNF, IL-6, IL-7, IL-1, and IL-23 promote the production of RANKL, which indirectly facilitates osteoclast formation. Conversely, certain cytokines like IL-3, IL-4, interferon-gamma (IFN-γ), IL-10, IL-18, and IL-33 exhibit anti-osteoclastogenic properties [3, 5, 8, 13]. Cell-cell fusion and multinucleation are crucial for the maturation of osteoclasts and their function in resorbing bone. Osteoclast fusion includes the processes of relocation, identification, intercellular adherence, and fusion of the membranes. After the fusion of the cell with mature osteoclast, single-nucleated precursors migrate to resorption sites [7] The fusion process necessitates the participation of multiple proteins, such as Atp6v0d2, dendritic cell-specific transmembrane protein (DC-STAMP), and osteoclast stimulatory transmembrane protein (OC-STAMP) [3,5,7,8,14]

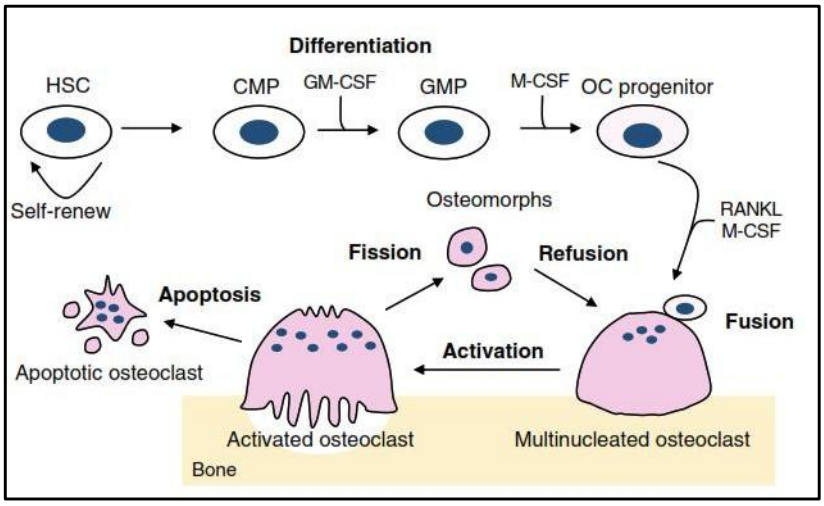

Figure 1. This diagram illustrates the development and specialization of osteoclasts. Hematopoietic stem cells (HSCs) produce common myeloid progenitors (CMPs). Upon granulocyte/macrophage colony-stimulating factor (GM-CSF) stimulation, CMPs develop into granulocyte/macrophage progenitors (GMPs). GMPs then progress into monocytes/macrophages stimulated by macrophage colony-stimulating factor (M-CSF). These monocytes/macrophages act as precursors for osteoclasts (OCs). Osteoclast progenitors travel through the bloodstream to bone surfaces, where they fuse and mature into multinucleated osteoclasts under the influence of M-CSF and receptor activator of NF-κB ligand (RANKL). Activated mature osteoclasts are essential for the resorption of bone matrix. Ultimately, they undergo apoptosis or are recycled through osteomorphs [3].

4. The Role of Osteoclasts in Bone Homeostasis

Alveolar tissue comprises hydroxyapatite crystals, ions, collagen, and proteins. To maintain alveolar bone homeostasis by regulating serum calcium levels, influenced by parathyroid hormone, calcitonin, and endocrine signaling. Changes in alveolar bone tissue are influenced by circulating calcium levels and nutritional and hormonal factors. Alveolar bone adjustments are influenced by osteoclasts responsible for resorption and osteoblasts for formation [1]

Bone coupling occurs within the basic multicellular unit and is a bone remodeling process in which bone resorption and formation are balanced to maintain bone hemostasis [3, 4, 11, 15]. Coupling is a direct engagement between osteoclasts and osteoblasts associated with the factors secreted from the bone matrix when bone resorption and the secretion of osteoclasts [4, 16]. The initial identification of coupling factors highlighted growth factors secreted from the matrix. Factors in the bone matrix influenced by bone resorption are transforming growth factor-β1 (TGF-β1) and insulin-like growth factor 1 (IGF-1). Osteoclasts activate TGF-β1 and then release it into the matrix in conjunction with its latency-associated propeptide (LAP). IGF-1 attaches to insulin-like growth factor-binding protein (IGFBP), a regulatory protein. Osteoblasts secrete IGF-1 when the bone matrix is being resorbed by osteoclasts [15, 16]

Remodeling is asynchronous within the basic multicellular unit (BMU), resulting in differential structural changes in cortical and trabecular bone across BMUs [7–9, 16, 17] As bone resorption occurs, TGF-β is secreted and acts as a signal that prompts the movement of bone mesenchymal stem cells (which are precursors of osteoblasts) to the resorption sites. This process ensures their availability within the Basic Multicellular Unit (BMU) where they differentiate into osteoblasts and form the bone. Therefore, the substances that are emitted by osteoclasts during the breaking down of bone are likely to attract and direct osteoblast precursors toward the surface of the bone. The regulation of bone differentiation and formation by these precursors is determined by the subsequent stages in the remodeling cycle [16]

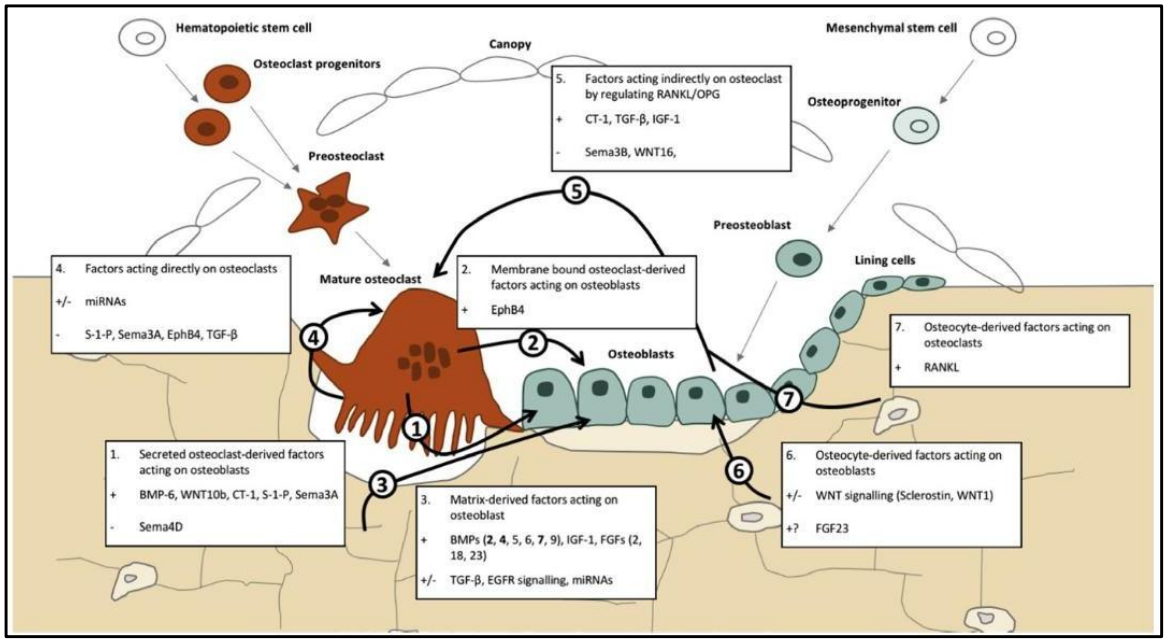

Figure 2. Illustrates the intricate dynamics between bone-resorbing and bone-forming cells in BMU. When the resorption phase occurs, osteoclasts release soluble factors (1) or release them from the bone matrix (3) to Howship's lacunae. These factors assist in synchronizing bone resorption and formation through osteoblast activity regulation. Osteoclasts also produce membrane-bound factors (2) that promptly impact osteoblasts. Certain factors secreted to Howship's lacunae have an autocrine effect on osteoclasts (4). Furthermore, osteoblasts (5) and osteocytes (7) indirectly influence osteoclasts indirectly via the expression of RANKL and/or OPG. Osteocytes in the bone matrix generate factors (6) and contribute to this coupling process [11]

4.1. Osteoclast-Mediated Bone Resorption

Osteoclastic bone resorption involves hydroxyapatite's dissolution and the bone matrix's degradation through proteolysis [3]. This process is facilitated by integrins and c- Src activation, triggered by RANKL, leading to reorganization of the cytoskeleton and accelerated fusion and resorption. Osteoclasts connect to bone matrix proteins by recognizing arginine glycine-aspartic acid (RGD) peptides by integrin αvβ3 receptor recognition, creating podosomes crucial for osteoclast resorption [18]. Podosomes form thick actin rings with a ruffled border, which allows enzymes like cathepsin K and protons to reach the bone surface and assist in bone resorption [3,4,10,19]

Cathepsin K facilitates the demineralization and degradation of collagen I-rich matrix structures by transporting protons and proteases via a ruffled border [3, 4, 19] On the ruffled border membrane, the H^+-ATPase deploys protons into the resorption lacuna, contributing to its acidification. Concurrently, chloride ions pass into this space through the CLCN7 chloride channel, also found on the ruffled border membrane, ensuring maintained electroneutrality. The functional secretion domain (FSD) on osteoclasts is responsible for endocytosis and the release of degradation products like collagen, protein fragments, calcium, and phosphate [3, 4]

The optimal bone resorption cycle involves cell detachment, migration, and resorption of the bone matrix, involving integrins. Osteoclasts deliver growth factors that increase osteoblast activity or recruit them to the resorption area [18]. Furthermore, recycling osteoclasts during bone resorption reduces energy costs associated with collecting precursors from circulatory systems and converting them into osteoblastic ones from a bioenergy perspective [20]. Following resorption, osteoclasts either enter apoptosis or prepare for subsequent bone resorption cycles [4]

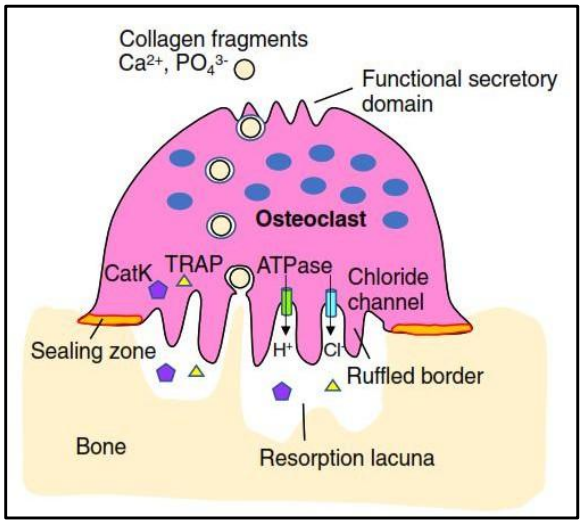

Figure 3. Osteoclasts, specialized in bone resorption, create ruffled borders and sealing zones to lower the pH of the resorption lacuna. Protons are actively transported into the lacuna by the vacuolar H+-ATPase situated at the ruffled border, while chloride channels facilitate the transport of chloride ions to maintain ionic balance. Cathepsin K and TRAP enzymes are released into the lacuna to break down the bone matrix. The degraded matrix components are subsequently absorbed at the ruffled border and discharged from the FSD [4]

4.2. Bone Remodeling Phase

The bone remodeling cycle has several phases: initialization, resorption, reversal, creation, and termination [7, 10, 11, 17, 21]

The initiation or activation phase is when an old or injured bone is substituted to facilitate remodeling. Osteocytes attract osteoclast precursor cells to move to the bone surface because of mechanical stress or micro-damage. Osteoclastogenic signals, like M- CSF and RANKL, facilitate differentiation, fusion, maturation, longevity, and activation of osteoclasts. Osteoblasts inhibit this process by releasing osteoprotegerin (OPG), which binds to RANKL, thereby preventing osteoclast formation and potentially regulating bone remodeling within the Basic Multicellular Unit (BMU). Osteocytes contribute to remodeling by producing sclerostin, suppressing Wnt signaling in osteoblasts. Additionally, nitric oxide and vascular endothelial growth factors are crucial in attracting and differentiating osteoclasts.

During the resorption phase, RANKL, M-CSF, and immunoglobulin-like receptor ligands produced by osteocytes and other cells in the osteoblast lineage initiate osteoclast formation. Fully developed osteoclasts establish Howship's lacunae, where they engage in matrix degradation and hydroxyapatite dissolution through proteolytic enzymes and proton transport. This process begins in an acidic environment that catalyzes mineral breakdown within bone tissue, releasing enzymes like MMPs and cathepsin K that break down the organic matrix.

The reversal phase of bone formation is characterized by removing exposed collagen fibrils, facilitated by mononuclear phagocytes or osteomacs during the transition of the basic multicellular unit (BMU). Osteoclasts produce extra vesicles, matrix- released, and secreted factors to create osteoblast lineages. When mature osteoclasts are not in contact with mature osteoblasts, it starts the resorption of bone; however, when they come into contact with mature osteoblasts during the revesal phase, they do not absorb the bone. The resorption phase is terminated by osteoblasts' production of OPG, which suppresses osteoclasts. The activity of bone formation increases as osteoblast-derived cells increase.

The next phase is the bone formation and termination phase. The procedure of bone formation requires cellular communication and differentiation, aided by growth factors, osteoclast products, and osteocyte signals. Osteoblasts

mineralize osteoid, depositing it as new bone. A new bone matrix is produced and mineralized to replace the void left by resorption [7, 11]

Mesenchymal stem cells (MSCs) transform into osteoblasts, which become osteocytes within bone, facilitating the creation of new bone tissue. BMP-2, released during bone resorption driven by osteoclasts, is essential in this process. BMP-2 binds to serine/threonine kinase receptors, initiating Smad and non-Smad signaling pathways. This activation triggers the expression of osteogenic genes such as Runt-Related Transcription Factor 2 (RUNX2) and Osterix (Osx). Additionally, BMP-2 promotes osteoclastogenesis by leading the differentiation of osteoclast precursor cells to become mature osteoclasts [22]. Osteocytes finalize the remodeling process by creating sclerostin, which prevents Wnt signaling in osteoblasts. After replacing comparable quantities of resorbed bone, mature osteoblasts, through apoptosis, change into a bone-lining phenotype and transform into osteocytes. It keeps the bone surface inactive until the next stage of remodeling [7, 11]

Oral biofilms, microbiota, and a balanced immune response affect alveolar bone homeostasis. Chronic inflammation may impair the "coupled" action between osteoclasts and osteoblasts, leading to bone destruction through RANKL, Notch, Wnt signaling, and the pyrine domain-containing receptor family 3 (NLRP3) receptors [1]

5. Osteoclasts Associated with Periodontitis

The integration of alveolar bone with teeth and its adjacency to dental plaque biofilms make it a unique tissue. Periodontal health depends on a well-regulated immune response to oral biofilms. Changes in biofilm arrangement can trigger inflammation in the epithelial and gingival connective tissues. Inflammatory immune cells that penetrate these tissues release specific factors that initiate signaling to bone cells through paracrine methods. Persistent inflammation over time disrupts the coordination between osteoclasts and osteoblasts, ultimately causing the breakdown of alveolar bone [9]

Periodontitis is a chronic inflammatory condition of the bone resulting from the excessive degradation of bone tissue by harmful oral bacteria, such as Porphyromonas gingivalis, Tannerella forsythensis, and Treponema denticola. Various bacterial infections lead to the loss of alveolar bone, which impacts the RANKL system. B and T lymphocytes substantially impact the development of bone resorptive lesions [3]. Neutrophils are prevalent leukocytes in the periodontium, essential for defense from microbes. They release inflammatory molecules that either promote bone resorption or prevent bone formation. Monocytes/macrophages have an essential function in both the breakdown and formation of bone. They display two clearly different phenotypes: one that promotes inflammation (M1) and one that promotes healing (M2). Based on a recent study, macrophages can simultaneously exhibit both the M1 and M2 phenotypes. The initial phases of osseous repair and osteoclastogenesis are triggered by M1 macrophages, which stimulate the production of substances that promote inflammation, such as IL-1, IL-6, IL-12, and TNF-α. IL-4 and IL-13 stimulate M2 macrophages to control inflammation and suppress osteoclast formation. Osteal macrophages, or osteomacs, assist bone remodeling by promoting osteoblast growth and enhancing bone formation [8] RANKL is synthesized by osteoblasts, periodontal ligament (PDL) cells, gingival epithelial cells, fibroblasts, and cementoblasts. Bacterial compounds like lipopolysaccharide (LPS) increase RANKL expression and stimulate proinflammatory cytokines from immune cells. Toll-like receptor 4 detects and interacts with LPS. TNF-α expression is regulated by LPS/TLR4, which in turn affects osteoclast differentiation. TNFR-2 enhances the osteoclastogenesis process induced by LPS and TNF-α. TLR2 signaling is an additional factor in bone loss facilitated by RANKL. This system can identify peptidoglycan and lipoteichoic acid originating from gram-positive bacteria, which have a role in the response to P. gingivalis [3, 4, 13]

6. Discussion

Alveolar bone homeostasis is crucial as it regulates serum calcium levels, which are regulated by parathyroid hormone and calcitonin. Furthermore, the metabolism of alveolar bone is impacted by endocrine signals, including sex hormones and circulating inflammatory factors [1]. According to a review by Hathaway-Schrader and Novince

(2021), mechanical studies indicate that functional strains in alveolar bone are estimated to be two to four times greater than those observed in skeletal sites outside the oral cavity. This suggests that occlusal stress, transferred via the fibrous junction of the periodontal ligament, has a significant function in the remodeling of alveolar bone [9]. According to Omi and Mishina, 2020, a possible reason for rapid bone remodeling could be the mechanical stimulation from chewing or mastication [3, 4]

Osteocytes, located within the bone matrix, respond to mechanical stress. Certain soluble molecules, such as Dickkopf-related protein 1 and Sclerostin, play significant roles in bone remodeling by inhibiting the Wnt/β-catenin pathway. This inhibition reduces bone formation and enhances osteoclast formation. Mechanical stress prompts osteoblasts to decrease the production of sclerostin and Dickkopf-related protein 1, thereby promoting accelerated bone formation [3, 11]. Furthermore, the inflammatory response in alveolar bone triggered by subgingival plaque leads to periodontal bone loss by increasing osteoclast activity and/or reducing osteoblastic activity [9]

Maintaining bone homeostasis requires coordination between osteoclasts, osteoblasts, and osteocytes through various molecular signaling pathways [3, 12] Osteoblasts and osteoclasts interact to regulate bone remodeling, with osteoclasts aiding in healing defects by secreting pro-osteogenic factors, while osteogenesis is negatively impacted by osteoclast depletion [23] To maintain bone homeostasis, various processes like osteoclast differentiation, cell fusion, and bone resorption must be integrated [24]

Osteoblast progenitor cells undergo differentiation, becoming fully functional osteoblasts and creating new ones within the bone remodeling unit (BMU). They can also transform into lining cells or osteocytes [11] Based on a review by Hathaway-Schrader and Novince, 2021, studies indicated that inflammation caused by plaque in the diet significantly influenced the activities of osteoclasts and osteoblasts in the BMU of periodontal tissues. Alveolar bone loss induced by experimental periodontitis was characterized by specific alterations in physiological bone remodeling: enhanced activation of bone cells triggering localized bone restructuring; escalated bone resorption mediated by osteoclasts; increased occurrence of reversal (resorption sites devoid of bone matrix and lined by mononuclear cells), and reduced bone formation mediated by osteoblasts [9]

Osteoblasts impact osteoclasts through various pathways such as OPG-RANKL- RANK; RANKL has a promotor effect on the osteoclast, while OPG is an osteoclast inhibitor. RANKL-LGR4-RANK pathways, Leucine-rich repeat-containing G-protein- coupled receptor 4 or LGR4, also a RANKL receptor, inhibit RANK binding to RANK. Ephrin2-ephB4 pathways: Ephrin2 is an inhibitor for osteoclasts. This pathway promotes osteoblast differentiation and, as a result, induces bone formation. Fas (Factor-associated suicide) - FasL signaling, which osteoblast stimulates osteoclast apoptosis. Additionally, osteoclasts are influenced by cytokines like IGF-1 and TGF-β [11, 12, 25]. According to a review by Sims and Martin, 2020, as osteoclasts and osteoblasts were cultivated, their direct interaction initiated reciprocal communication between the cells. The ephrinB2 protein derived from osteoclasts interacted with EphB4 receptors on osteoblasts, generating signaling pathways that stimulated bone production. On the other hand, this connection also caused osteoclast differentiation through reverse signaling mediated by the ephrinB2 ligand [16]

Cell-to-cell communication between osteoblasts and osteoclasts facilitates bidirectional signal transduction during osteoclast differentiation and maturation. Ephrin B2 inhibits the FOS/NFATc1 axis, suppressing osteoclast differentiation, while forward signaling stimulates it. SEMA3A, synthesized by osteoblast lineage cells, promotes the formation of the bone via the WNT/β-catenin pathway. Meanwhile, Sema4D, expressed by osteoclast, prevents bone formation.[25] Osteoclasts promote bone formation by releasing vesicles enriched with RANK, which activates the runt-related transcription factor 2 (RUNX2). This enhances the maturation of osteoclasts, thereby stimulating osteoclast differentiation and bone degradation. This process is crucial for maintaining bone homeostasis [7, 12]

After an equivalent quantity of bone has been resorbed and replaced, the remodeling cycle ends. After the process of mineralization, mature osteoblasts may enter apoptosis, transition to a bone-lining state, or integrate into the mineralized matrix, eventually differentiating into osteocytes. The bone surface returns to a resting state, maintaining this environment until the next remodeling cycle begins [3].

7. Conclusion

Alveolar bone homeostasis is intricately regulated by hormonal signals, mechanical forces, inflammatory responses, and cell-to-cell communication pathways involving osteoblasts, osteoclasts, and osteocytes. This study focuses on osteoclasts' significance, including their biology, differentiation, activation, and factors influencing their activity in alveolar bone for maintaining bone homeostasis and remodeling conditions through bone resorption. Furthermore, the correlation between osteoclasts and periodontitis, and its effect on excessive osteoclast activity. Understanding osteoclast biology is crucial in pathological conditions like periodontitis, leading to significant clinical implications. Continued research will further advance our ability to develop effective treatments for bone-related conditions, including alveolar bone and periodontitis.

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