PAPER – OPEN ACCESS

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Author : Edward Gozali, and Aini Hariyani Nasution
DOI : 10.32734/tm.v2i1.2681
Electronic ISSN : 1234-1234
Print ISSN : 1234-5678

Volume 2 Issue 3 – 2025 TALENTA Conference Series: Tropical Medicine (TM)

TM Conference Series 02 (2025)
TALENTA Conference Series
Available online at https://talentaconfseries.usu.ac.id

Role Of Osteoblast in Alveolar Bone Formation

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Abstract

Background: Bone remodeling is a dynamic process involving the regulated breakdown of residual bone and is essential for maintaining bone balance and structural integrity. Objective: This study aimed to examine the roles of osteoblasts and osteoclasts in alveolar bone formation and their interactions in the bone remodeling process. Subject: Discussion Osteoclasts, derived from monocytes/macrophages, primarily assist in bone resorption by secreting hydrochloric acid and proteolytic enzymes. In contrast, osteoblasts are distinct from mesenchymal stem cells and have dual functions in bone matrix formation and regulation of mineralization. The critical interactions between osteoblasts and osteoclasts, facilitated by direct cell-to-cell contact, cytokines, and extracellular matrix interactions, are critical for successful bone remodeling. Osteoblasts can influence osteoclast development, differentiation, or apoptosis; conversely, osteoclasts can interfere with osteoblast activity. Many signaling pathways regulate osteoblast and osteoclast functions, including the OPG/RANKL/RANK, Wnt, Hedgehog, BMP, TGF-β, and Notch pathways. Conclusion: In summary, the complex interactions between osteoblasts and osteoclasts are essential for maintaining bone balance and undergoing remodeling. Understanding the functions of these cells and their signaling pathways provides invaluable insight into the processes involved in bone production and resorption. Additional investigations in this domain may be important in advancing innovative therapeutic strategies for bone-related disorders, such as osteoporosis.

Keywords: Osteoblast; osteoclast; bone formation; bone resorption; bone remodeling

1. Introduction

For bones to remain healthy throughout life, a complex and ever-changing process of bone remodeling must be carried out simultaneously by osteoclasts and osteoblasts [1]. This process is essential to building, growing, and maintaining a strong skeletal structure. There are four separate steps in remodeling: activation, resorption, reversion, and formation. When osteoclasts enzymatically break down bone minerals and matrix during the resorption phase, growth mediators are released, stimulating osteoblasts to begin the process of new bone formation [2]. During the formative phase, osteoblasts produce matrix proteins such as type I collagen and proteoglycans. These proteins are then mineralized to form fully-grown bone tissue. Optimal bone health is achieved when multiple signaling pathways and local factors regulate the perfect balance between bone resorption and formation. To effectively treat bone diseases and disorders, researchers must thoroughly understand osteoblast activity during alveolar bone production [3]. This paper aims to provide a synopsis of alveolar bone remodeling and highlight the role of osteoblasts in this process. This includes examining the mechanisms that activate osteoblasts to promote bone regeneration actively.

Selection and peer-review under responsibility of Seminar Periodental Update 5 2024
p-ISSN: 1234-5678, e-ISSN: 1234-1234, DOI: 10.32734/tm.v2i1.2681

2. Bone Remodelling

Bone remodeling is governed by two key processes: osteoclast-mediated bone resorption and the subsequent activation of osteoblasts to create new bone. This carefully regulated cycle, involving both cell types, is divided into four stages: activation, resorption, reversal, and formation. A basic multicellular unit (BMU), consisting of osteoclasts, osteoblast precursors, and mature osteoblasts, manages this process [1,2]. Local factors such as microdamage or inflammation can initiate remodeling by encouraging osteocytes to emit signals that promote bone resorption [3]. Another significant factor is osteocyte death, which may result from microdamage or immune cell activity, leading to the release of factors that stimulate osteoclast activity [4]. Additionally, remodeling can be initiated by local or systemic signals, including parathyroid hormone (PTH) [5].

In humans, bone resorption in the basic multicellular unit (BMU) typically occurs over about 3 weeks, followed by a phase of bone production that lasts 3 to 4 months [1,2]. During the resorption process, osteoclasts release signals such as IGF-1 and TGF-β from the bone matrix, facilitating osteoblasts' attraction and activation. Once resorption is complete, osteoclasts undergo apoptosis, which initiates the reversal phase. During this phase, osteoclasts undergoing apoptosis release chemotactic mediators, such as CXCL16, CCL5, CCL20, and CCL12, along with TGF-β, which attract mesenchymal cells generated from the stroma to the repair site. Furthermore, osteoblastic cells release CCL2, which is believed to facilitate the recruitment of osteoprogenitor cells [6]. These progenitor cells then colonize the reabsorbed bone surface and undergo differentiation into osteoblasts, a process influenced by factors such as BMP and Wnt, which occur in the periodontal and iliac bones [7]. As bone develops, a number of proteins are produced, such as alkaline phosphatase, proteoglycans, glycosaminoglycans, osteonectin, osteopontin, osteocalcin, and class I collagen. Osteocalcin production occurs during bone formation by osteoblasts. Osteocalcin is the most abundant non-collagenous protein in bone. Its primary role is to bind collagen fibers and apatite crystals, allowing mineralization to occur. One of the natural mineralization inhibitors, inorganic pyrophosphate, is broken down by alkaline phosphatase to aid mineralization. Hydroxyapatite, an inorganic phosphate mineral, is produced during this breakdown process. The proteins osteonectin and osteopontin play important roles in mineral precipitation and crystallization, energy dissipation, and prevention of microfracture propagation in bone. [8].

3. Bone Remodelling

Progenitor cells derived from the monocyte/macrophage lineage aggregate into multinucleated cells called osteoclasts. A sealing zone is formed as podosomes help them bind to the bone surface. This zone then creates an acidic microenvironment. This osteoclast configuration breaks down the bone matrix with the help of proteolytic enzymes such as cathepsin K and dissolves bone minerals with hydrochloric acid. [2].

The primary signaling pathways that regulate osteoclast function include: [2]

- Macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κB ligand (RANKL) both initiate the differentiation process. Osteoclast precursor cells can undergo osteoclast differentiation after binding RANKL to the RANK receptor located on their front surface.
- Osteoblast regulation is mediated by osteoprotegerin (OPG), a decoy receptor that binds RANKL, inhibiting its interaction with the RANK receptor on osteoclast precursors. This inhibitory mechanism effectively regulates osteoclastogenesis by limiting the formation and activation of osteoclasts.
- Inflammatory Induction: Immune cells can trigger osteoclastogenesis under inflammatory conditions like rheumatoid arthritis. This occurs due to elevated RANKL production, which promotes the formation of osteoclasts and increases bone resorption.

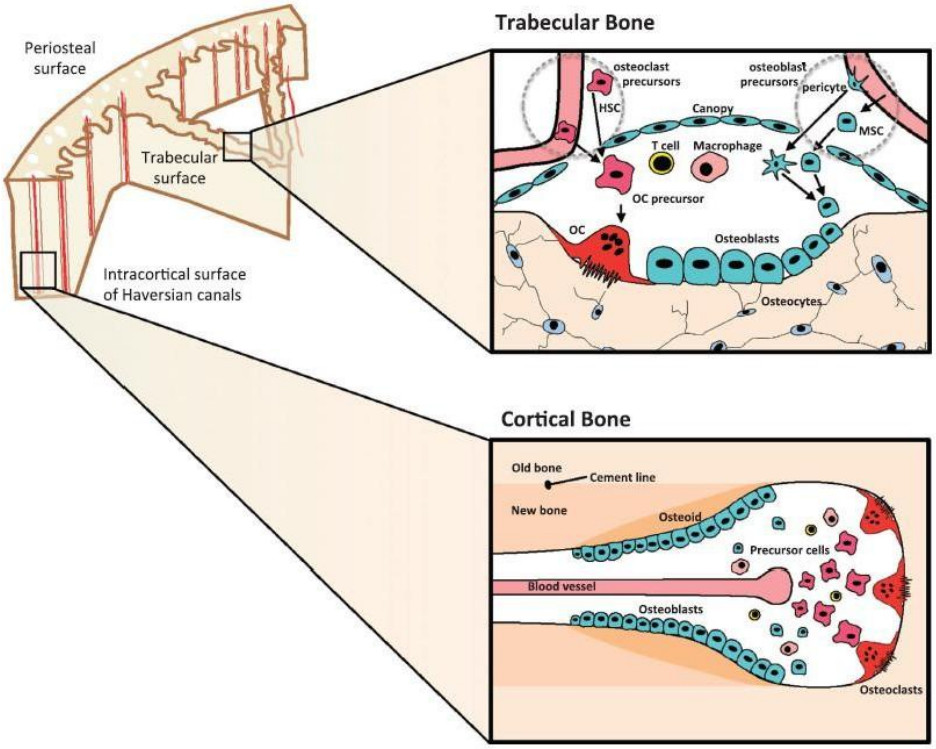

Figure 1. Bone remodeling begins in the bone remodeling compartment (BRC), located beneath the cell layer lining the trabecular bone (top panel) or within the Haversian canals of the cortical bone (bottom panel). Osteoclasts (OC) proliferate from hematopoietic precursors (HSCs) derived from the bone marrow and circulatory system. Furthermore, osteoblast precursors originate from mesenchymal stem cells (MSCs) in the bone marrow, circulatory system, or pericytes. Within the basic multicellular unit (BMU), these precursors undergo differentiation, developing from osteoblast precursors into fully functional osteoblasts responsible for bone synthesis, and can then differentiate into osteocytes. Furthermore, lining cells can differentiate into active osteoblasts. T lymphocytes and macrophages can potentially reach the BRC via the circulatory system. [2].

4. Bone Resorption by Osteoclast

Osteoclastic bone resorption involves the dissolution of hydroxyapatite via acid secretion and the breakdown of the bone matrix through proteolysis [9]. This process begins when multinuclear osteoclasts adhere to the bone surface. Reorganization of the osteoclast cytoskeleton, which facilitates fusion and resorption, is caused by the activation of c-Src, a kinase induced by RANKL, and integrins, which facilitate contact. Bone matrix proteins contain the peptide arginine-glycine-aspartic acid (RGD), which osteoclasts can bind with its integrin αvβ3. Together with actin-binding proteins such as talin and vinculin, αvβ3 is essential for osteoclast resorption because it forms numerous podosomes surrounding the F-actin core and facilitates osteoclast attachment [10]. The formation of a wavy border occurs when these podosomes fuse into a tight actin ring [9]. For resorption through tunnels, a wavy border is required. Bone resorption is accelerated because it provides protons and collagenolytic enzymes such as cathepsin K to the bone surface. The ruffled border is responsible for transporting protons and proteases, including cathepsin K, which helps demineralize the bone matrix and decompose the collagen I-rich matrix [9]. Osteoclasts have a functional secretory domain (FSD) on the basolateral membrane that they use to take up and release degradation products such as proteins, calcium, phosphate, and collagen fragments. The resorption process can result in osteoclasts forming circular pits or extended tunnels in the bone matrix. Trench-forming osteoclasts generally show higher aggressiveness and continuity than pit-forming osteoclasts. Differences in resorption

mechanisms can be influenced by variables such as precursor source, location in the skeletal system, gender, or the degree of systematic and local regulation. Due to its larger surface area in direct contact with the bone marrow and bloodstream, trabecular bone undergoes resorption along the skeletal surface, whereas cortical bone resorption occurs through tunnels [9].

For bone resorption to function properly, cells must first migrate to the resorption site, degrade the underlying bone matrix, dissociate, and then migrate to the new location. Integrins are critical in this process. Release of growth factors integrated into the bone matrix occurs during osteoclast-mediated bone resorption. These substances attract osteoblasts to the resorption site or enhance their activity [10]. After completing resorption, osteoclasts undergo apoptosis or begin another resorption cycle. From a bioenergetic perspective, recycling osteoclasts helps conserve energy by reducing the need to recruit and differentiate new precursor cells from circulation, thus preserving resources that would be otherwise expended if osteoclasts undergo apoptosis [11].

5. Osteoblast

Although osteoblasts can be produced from chondrocytes, bone lining cells, or mesenchymal stem cells, the latter two sources are less common. Osteoblasts rapidly produce osteoid, the unmineralized bone matrix, thanks to the Golgi apparatus and the endoplasmic reticulum, which are present when the cells are active. The fate of osteoblasts can be one of three possible states: cell death (apoptosis), differentiation into bone lining cells, or differentiation into osteocytes embedded in the bone matrix. A bone matrix rich in type I collagen is secreted, and these cells largely control the mineralization of this matrix. [2].

Key signaling pathways that regulate osteoblast development and function include: [2]

Transcription factors SOX9 and Runx2, present in all osteoblast progenitor cells, are critical in initiating osteoblast development. Operating System X (OSX): The zinc finger transcription factor OSX regulates the transition from osteoprogenitors to preosteoblasts; it operates downstream of Runx2. Protein signaling through the Wnt pathway: The canonical Wnt signaling pathway must be activated for osteoblastogenesis to occur. Accumulation of β-catenin in the nucleus occurs when proteins belonging to the Wnt family interact with the Frizzled receptor and coreceptors, such as LRP5/6, which are members of the LDL receptor-related protein family. Directing osteoblast formation from mesenchymal progenitors is an important function of this nuclear β-catenin. Osteocytes produce proteins, including Sclerostin (SOST) and members of the Dickkopf family (DKK), that suppress Wnt responses and are released to control this pathway. Several cellular signaling channels, including the Hedgehog protein, NOTCH, FGF, and BMP signaling pathways, significantly influence the control of osteoblastogenesis. This signaling network synchronizes the complex processes of osteoblast differentiation and function to efficiently build and maintain bone in response to developmental cues and environmental stimuli.

6. Osteoblast - Stimulating Bone Formation

Several pathways play critical roles in stimulating osteoblasts to promote bone formation. These pathways include: [12]

- Wnt Signaling: Wnt proteins initiate signaling pathways that regulate osteoblast differentiation and function. Activation of Wnt signaling typically promotes bone formation.
- Hedgehog Signaling: Hedgehog proteins, such as Sonic Hedgehog, play a role in skeletal development and fracture repair by modulating osteoblast proliferation and differentiation.
- Bone Morphogenetic Protein (BMP) Signaling: Body matrix proteins (BMPs) are growth factors that stimulate osteoblast development and bone formation. They play a critical role in adult embryonic bone formation and bone preservation.
- Transforming Growth Factor β (TGF-β) Signaling: Members of the trigeminal factor-β family control several aspects of bone metabolism, such as osteoblast differentiation and matrix production.

- Notch Signaling: The Notch signaling pathway regulates osteoblast differentiation and bone remodeling processes, thereby influencing bone formation.

These pathways interact with each other and with other signaling molecules to orchestrate the complex processes involved in bone development, growth, maintenance, and repair [12].

Wnt are secreted glycoproteins that activate signaling systems required for bone formation. The primary means by which this is achieved is by stimulating osteoblast activity, facilitated by β-catenin, a transcription factor. The Wnt/β-catenin pathway heavily influences the regulation of embryonic development and bone formation. More than twenty molecules, referred to as Wnt-1 to Wnt-16b, make up the Wnt ligand repertoire. Ten different frizzled receptors mediate the effects of these ligands. Wnt signaling can be triggered by co-receptors such as lipoprotein receptor-related protein (LRP)-5 or LRP-6. The proliferation of precursor cells, differentiation and survival of osteoblasts, and overall cellular homeostasis are all promoted by the Wnt signaling pathway, which plays a critical role in bone remodeling and preservation [13].

The FGF family includes many growth factors that are essential for bone development. To enhance bone formation, fibroblast growth factor 2 (FGF2)—also called basic FGF—increases osteoprogenitor cell proliferation, promotes angiogenesis, and enhances osteoblast differentiation. In addition, FGF2 increases BMP2 signaling and higher β-catenin protein levels in calvarial osteoblast progenitors. Because it increases RANKL synthesis in osteoblasts, FGF-18 is also involved in bone remodeling [14].

Both IGF-1 and IGF-2 are major types of Insulin-like Growth Factors. The local and systemic actions of IGF-1 are enabled by its binding to its receptor on the cell surface. Some of these functions include preventing cell death, promoting bone tissue growth, and increasing the number of osteoblast precursors. As a result, it promotes bone production and helps maintain bone mass. The job of osteoblasts, osteocytes, preosteoblasts, and osteoclasts is to make IGF-1. Osteoclast differentiation is also influenced by IGF-1 signaling. IGF-2, especially important during fetal development, controls growth and maintains stem cell populations in various organs. [15].

Of the nearly 30 members that make up the TGF-β superfamily, you can find nodal, activin, several bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), and three isoforms of transforming growth factor-β (TFGF-β1, TGF-β2, and TGF-β3). Simply put, these compounds are essential for controlling bone cells' growth, differentiation, and activity. The main intracellular effectors of TGF-β signaling are the SMAD proteins. To be more specific, TGF-β1 stimulates the development of osteoprogenitors by activating the ERK pathway and the transcription factor Runx2, both of which are required for osteoblast differentiation. According to reference 16, transgerminal factor-β2 (TGF-β2) is essential during embryonic development. When BMP2 and TGF-β work together, mesenchymal stem cells can more easily differentiate into mature osteoblasts. Natural human mesenchymal stem cells (HMSCs), attracted by TGF-β3, can initiate the process of bone remodeling. Endochondral bone formation is another process involving TGF-β3. Beta-morphine peptides (BMPs), which are members of the TGF-β superfamily, inhibit the proliferation of mesenchymal stem cells into osteoblasts and enhance their differentiation into these cells through Wnt signaling. Several types of cells, including osteocytes and osteoblasts, produce biological matrix proteins (BMPs). Importantly, BMP-2 and BMP-7 have been extensively studied for their functions in the bone formation process. BMP-2, after being released from the bone matrix during resorption, promotes osteoblast development through stimulation of Runx2 expression. BMP-7 signaling facilitates osteoblast commitment to a specific lineage and promotes bone development in anatomical structures, including the femur and tibia [17].

Sonic hedgehog (Shh) and Indian hedgehog (Ihh) proteins promote bone growth. Shh and Ihh agonists stimulate osteoblast differentiation and augment bone growth. More precisely, Ihh stimulation facilitates the transformation of mesenchymal stem cells (MSCs) into osteoblasts and suppresses their transformation into adipocytes. In addition, the Wnt and BMP pathways work with Ihh signaling to support the bone production process [18]. Osterox is an essential transcription factor exclusive to osteoblasts, and Shh inhibits its expression. This increased expression triggers the activation of genes important for the differentiation of immature osteoblasts into mature osteoblasts [19]. Furthermore, Shh can enhance periodontal regeneration by activating the development of cementoblasts,

which are cells essential for producing cementum around the tooth root. Taken together, Ihh and Shh demonstrate how hedgehog proteins are part of a complex regulatory network that regulates bone genesis, development, and repair [4].

The Notch signaling pathway, which usually inhibits bone formation, is activated by cell-cell interactions. The five Notch ligands found in mammals are Jagged 1 and 2, Delta-like 1, 3, and 4. Notch receptors 1, 2, 3, and 4 bind specifically to the ligands, which are transmembrane proteins. Notch-1 and Notch-2 mediate the inhibition of mesenchymal progenitor differentiation into osteoblasts [20]. Notch signaling also prevents mesenchymal stem cells (MSCs) from differentiating into osteoblasts by suppressing the Wnt pathway. By increasing the synthesis of osteocyte Sost and Dkk1, Notch-1 signaling preferentially inhibits femoral bone development. Notch-1 and Notch-2 can stimulate osteoprotegerin (OPG) production in osteoblasts and osteocytes to inhibit osteoclastogenesis through direct interactions and indirect pathways. Osteoclast formation and activity are reduced because OPG acts as a rogue receptor for RANKL, which stands for Receptor Activator of Nuclear Factor κB Ligand. On the other hand, Notch-3 promotes osteoclastogenesis and bone resorption by increasing RANKL expression in osteocytes and osteoblasts [21]. Notch signaling influences bone homeostasis in multiple ways through its interactions with other signaling pathways, such as Wnt and RANKL/OPG, and modulation of osteoblast and osteoclast development.

In addition to the well-known factors involved in bone formation and coupling, several others play significant roles, as reviewed recently: [22]

- Platelet-Derived Growth Factor (PDGF): Periodontal ligament growth factor (PDGF) promotes the proliferation of osteoblast precursors and enhances periodontal bone formation in vivo. This growth factor significantly impacts the bone remodeling process because it regulates cell proliferation and division. [23].
- Semaphorins: A heterogeneous group of extracellular signaling molecules known as semaphorins exert diverse effects on bone. Sema3A and Sema3B are critical in maintaining bone mass by suppressing bone resorption and facilitating bone growth. These molecules are crucial for mediating cellular interactions and tissue patterning during development and maintaining bone homeostasis [24].

These factors highlight the complexity and interplay of signaling pathways involved in bone metabolism, demonstrating their diverse roles in regulating bone formation and remodeling processes [22].

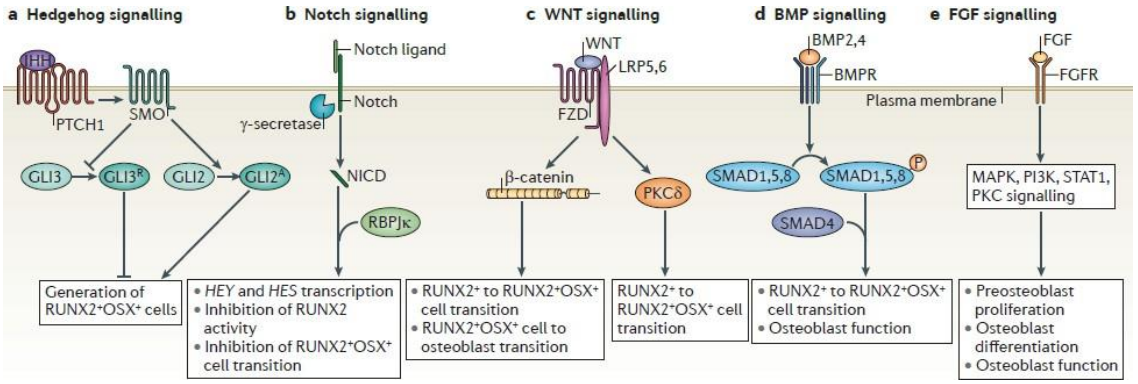

Figure 2. Several pathways are critical in stimulating osteoblasts to promote bone formation [25].

7. The Interaction Between Osteoblast and Osteoclast

The interaction between osteoblasts and osteoclasts is essential for maintaining bone homeostasis and facilitating bone remodeling. Below are some key points regarding their interplay: [26].

- Communication between osteoblasts and osteoclasts enables synchronized bone remodeling and maintenance of homeostasis through cell-cell contact, cytokine production, and interactions with the extracellular matrix.

- Several pathways, including OPG/RANKL/RANK, RANKL/LGR4/RANK, Ephrin2/ephB4, and Fas/FasL, enable osteoblasts to control bone resorption and maintain bone homeostasis. These pathways also influence osteoclast formation, differentiation, and death.
- The atp6v0d2 isoform of the vacuolar (H+) ATPase (v-ATPase) V0 domain, semaphorin 4D, microRNA, complement component 3a, and osteoclasts all play a role in the process of bone production by osteoblasts. The regulation of bone remodeling is aided by these processes when carried out together. Osteoblast activity is regulated by cytokines produced from the reabsorbed bone matrix, such as TGF-β and IGF-1. This, in turn, stimulates bone synthesis and affects the entire bone turnover process.
- Osteoblasts inhibit osteoclast differentiation by inhibiting osteoclast stimulation and activating the Ephrin2/EphB4 pathway through osteoprotegerin (OPG) synthesis, a mimic receptor for RANKL.
- During bone turnover, osteoclasts release monocyte chemoattractant protein-1 (MCP-1) and macrophage colony-stimulating factor (M-CSF), which enhance osteoblast recruitment and activity.
- RANKL, expressed by osteoblasts, binds to the RANK receptor on osteoclasts, triggering downstream signaling pathways that regulate osteoclast growth, differentiation, and bone resorption activity. • Osteoblasts can induce osteoclast apoptosis by expressing Fas ligand (FasL), which binds to the Fas receptor on osteoclasts, leading to programmed cell death.
- Osteoclasts can inhibit bone formation by secreting the d2 isoform of the vacuolar (H+) ATPase (v-ATPase) V0 domain (Atp6v0d2), semaphorin 4D, sclerostin, and various microRNAs or exosomes, which affect osteoblast activity and bone remodeling.
- Understanding how osteoblasts and osteoclasts interact is critical for developing drugs to treat bone-related disorders like osteoporosis.

8. Discussion

Osteoblasts and osteoclasts have complex interactions essential for enzymatic remodeling and maintenance of bone homeostasis. Mesenchymal stem cells differentiate into osteoblasts, which control the mineralization of the bone matrix. Osteoclasts, a subset of monocytes and macrophages, are important in bone resorption. For bone remodeling to be well-regulated, their communication—assisted by cytokines, interactions with the extracellular matrix, and direct cell-to-cell contact—must be effective [2].

Osteoblast and osteoclast activity cannot be modulated without important signaling pathways such as Wnt, Hedgehog, BMP, TGF-β, and Notch. Hedgehog proteins accelerate osteoblast development and enhance bone formation, while Wnt signaling drives both processes. During the differentiation of MSCs into osteoblasts, bone morphogenetic proteins (BMPs) are essential. The ERK pathway is activated by TGF-β, which actively promotes the growth of specialized osteoprogenitors. However, the Notch signaling system inhibits the development of MSCs into osteoblasts, reducing bone formation. [12].

Synchronized osteoclast and osteoblast activity is essential for ongoing bone tissue regeneration after remodeling. Osteoclasts secrete factors, including IGF-1 and TGF-β, from the bone matrix during the resorption phase, targeting and stimulating osteoblasts. Osteoclast apoptosis terminates bone resorption, initiating the reversal phase. At this stage, apoptotic osteoclasts use chemotactic signals to attract mesenchymal cells derived from the stroma to the repair site. Subsequently, these precursor cells differentiate into osteoblasts, producing type I collagen, proteoglycans, and other matrix proteins that mineralize and produce fully developed bone tissue. [26].

Developing effective treatments for bone-related disorders such as osteoporosis depends on our ability to understand the function of osteoblasts and osteoclasts in alveolar bone formation. Bone health and disease prevention depend on regulating the balance between bone formation and resorption. Future therapies for bone disease may result from further investigation of the signaling networks that control osteoblast differentiation and bone formation. [26].

9. Conclusion

The essential function of osteoblasts in alveolar bone development is to maintain the structural integrity of the alveolar bone. Osteoblasts are derived from mesenchymal stem cells; they are responsible for making the bone matrix rich in type I collagen, which is essential for bone mineralization and formation. The breakdown process is made possible by the complementary actions of osteoclasts and osteoblasts, which allow for the continuous rebuilding of bone. Developing successful therapeutic methods for bone- related disorders depends on our ability to gain insight into the signaling processes involved in osteoblast differentiation and bone production. The delicate balance between bone resorption and production underscores the need for careful control to maintain bone health and combat conditions such as osteoporosis.

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