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Review Article

FACTORS GOVERNING ALVEOLAR BONE REMODELING

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ABSTRACT

Bones are dynamic, viable, highly organised living tissue and is the main constituent of musculoskeletal system. Though the main function of bones is to protect the internal structures and to provide support to various soft tissues, additionally they also provide haematopoiesis in bone marrow. Bone constantly responds to the varying functional demands through continuous adaptation. This process of adaptation is known as 'remodeling'. Bone modeling is a result of a balance between bone formation by osteoblasts and bone resorption by osteoclasts. It is a continuous process and at any given time approximately 5-25% of bone surface undergoes remodeling. As normal physiological bone remodeling is imperative for the maintenance of bone strength and integrity, any imbalance, will either lead to increase or decrease in bone mass. Significant understanding of the interplay between different factors governing bone remodelling will potentiate better treatment options for pathologies involving the hard tissue.

INTRODUCTION

Alveolar bone is constantly being remodelled to adapt to changes in occlusal load. Alterations in resorption and repair and the interplay of these two phenomena are known as remodeling. [1] Bone remodeling is an active and dynamic process potentiated by the processes of bone deposition by osteoblasts and bone resorption by osteoclasts in correct balance. There is constant remodeling in all the bones of the body in response to various stimuli.[2]At a typical remodeling site, termed basic multicellular unit (BMU), specialized osteoclasts first remove bone over a period of approximately three weeks. The resulting resorption lacuna is subsequently filled by osteoblasts, a process lasting about three months.[3]

The bone remodeling cycle maintains the integrity of the skeleton through the balanced activities of its constituent cell types. Harold Frost in his research has shown that tight control of bone remodeling at the level of the BMU throughout the skeleton is essential to maintain structural integrity. The various phases of bone remodeling, the cells involved in the remodeling process, the various regulators of bone remodeling and the pathophysiology of bone remodeling are further discussed in this article.

The Bone Remodeling Process

The process takes place within bone cavities that need to be remodeled. In these cavities, there is the formation of temporary anatomical structures called basic multicellular units (**BMUs**), which are comprised of a group of osteoclasts ahead forming the cutting cone and a group of osteoblasts behind forming the closing cone, associated with blood vessels and the peripheral innervations. It has been suggested that BMU is covered by a canopy of cells (possibly bone lining cells) that form the bone remodeling compartment (**BRC**).[4] The BRC seems to be connected to bone lining cells on bone surface, which in turn are in communication with osteocytes enclosed within the bone matrix.

Phases of Bone Remodeling

Activation*:* The interaction between cells of the osteoblastic and hematopoietic system leads to the initiation of osteoclastic bone resorption. Fibroblasts secrete collagenase and other

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matrix-destroying enzymes, leading to altered tissue integrity. Osteoblastic cells can activate hematopoietic cells to differentiate into bone resorbing osteoclasts through the production of macrophage colony stimulating factor (M-CSF) and receptor activator of NFB ligand (RANKL). Lining cells of osteoblastic origin on the bone surface may also play a role by secreting proteolytic enzymes that remove a protein layer which normally covers the mineralized matrix.

Resorption: Osteoclasts bind to the mineralized matrix through vitronectin receptors and then form their resorbing apparatus, which secrete hydrogen ions and matrix degrading enzymes, particularly Cathepsin K. This permits the establishment of a low pH and a high concentration of enzymes that can degrade collagen quite effectively at that low pH. In addition to this cellular compartmentalization there may be a compartmentalization of the entire bone remodeling unit because the lining cells remain intact above the osteoclastic resorption sites and osteoblastic formation sites. This might allow for growth factors released from osteoclasts or matrix during resorption to be retained for longer periods and at more effective concentrations during the next phase.

Reversal*:* After osteoclastic resorption is complete there is a reversal phase during which mononuclear cells, which may be either of the mesenchymal or hematopoietic lineages, complete the removal of matrix and prepares the bone for formation by laying down a "cement line" of non-collagen proteins.

Formation: In the formation phase osteoblasts lay down matrix, which becomes gradually mineralized. As each layer of osteoblasts form its assigned amount of matrix it either undergoes apoptosis, or becomes buried in the matrix as an osteocyte. As this process of replacing the resorption cavity is completed, some of the osteoblasts may remain on the surface as lining cells.

Regulators of Bone Remodeling

The regulation of bone remodeling is both systemic and local which maintains the balance between bone resorption and bone formation.

Table 1 The critical mediators of Bone Resorption are listed below

Stimulators	Inhibitors
Interleukin – 1 (IL-1)	Interferon gamma (IFN-ɣ)
Interleukin – 6 (IL-6)	Osteoprotegerin (OPG)
Tumor Necrosis Factor (TNF)	Estrogens
Parathyroid Hormone (PTH)	Androgens
PTH-related Protein (PTHrP)	Calcitonin (CT)
Prostaglandin E2 (PGE2)	Cyclosporin
Macrophage Colony Stimulating Factor (M-CSF)	
Receptor Activator of NFκB (RANK)	
RANK Ligand (RANKL)	
1,25 Dihydroxy Vitamin D3 (Vitamin D)	

Growth Factors

These are polypeptides produced by the bone cells themselves which act as modulators of the cellular functions, fundamentally growth, differentiation, and proliferation.

IGF - I and II (Insulin- Like Growth Factor I and II)

These are polypeptides similar to insulin; they are synthesized by the liver and osteoblasts and found in high concentrations in the osteoid matrix.[5] They increase the number and function of the osteoblasts, stimulating collagen synthesis. Growth hormone, estrogens, and progesterone increase their production, while the glucocort icoids inhibit it. They also participate in the osteoblast osteoclast interaction and actively participate in bone remodeling.[6]

Transforming growth factor - β (TGF- β) TGF- β is a potent stimulator of bone formation, promoting osteoblastic differentiation and the synthesis of the osteoid matrix and inhibiting the synthesis of the proteases, especially the matrix metalloproteinase (*MMP*), an enzyme which degrades it.[7] TGF- β inhibits resorption on reducing the formation and differentiation of the osteoclasts, as well as mature osteoclast activity, and stimulating their apoptosis.[8]

Bone morphogenetic proteins (BMP) are included in the TGF- β family and are considered osteoinductive.[9] They stimulate the differentiation of the stem cells toward different cell lines (adipose tissue, cartilage, and bone). They are highly abundant in bone tissue and they strongly promote osteoblastic differentiation and are believed to inhibit osteoclastogenesis in addition to stimulating osteogenesis.[10]

Platelet - derived growth factor (PDGF), stimulates protein synthesis brought about by the osteoblasts, and, on the other, favors bone resorption. Other effects are the proliferation of fibroblasts and smooth muscle cells, neovascularization, and collagen synthesis. [11]

Fibroblastic growth factor (FGF) has an anabolic effect on bone, as it is a mitogen of osteoblasts, vascular endothelial cells, and fibroblasts.

Vascular endothelial growth factor (VEGF) induces angiogenesis and vascular endothelial proliferation. It produces vasodilation and an increase in vascular permeability. It is produced in hypoxia and is currently considered one of the key factors in the first phases of fracture repair and bone regeneration, as well as in tumor growth.

Granulocyte / macrophage - colony stimulating factor (GM-CSF) is important in osteoclastogenesis and may play a role in the pathogenesis of osteopetrosis.

Tumor Necrosis Factor (TNF) in vitro stimulates resorption and has been related with bone loss in arthritis and periodontal disease.

Matrix Proteins

The matrix proteins act as potential growth factor modulators.[12] These proteins participate in the regulation of the differentiation of the cells contained within the matrix. Collagen I is one of the earliest markers which regulates the osteoprogenitor cells, and alkaline phosphatase is a surface protein that could participate in the regulation of the proliferation, migration, and differentiation of the osteoblastic

cells. Osteonectin, fibronectin, and osteocalcin promote cell attachment, facilitate cell migration, and activate cells.

Cytokines

The cytokines like Interleukin 1 (*IL-1*), IL-6, IL-11, prostaglandin E2, Leukotrienes are important in bone remodelingdirectly stimulates osteoclastic resorption, increasing the proliferation and differentiation of the preosteoblasts, as well as the osteoclastic activity, and inhibiting the apoptosis of the osteoclasts.[13]

Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are members of a family of zinc-dependent proteolytic enzymes. Several MMPs expressed in the skeleton appear to function in endochondral ossification during embryonic development and in modeling and remodeling of bone post natally and later in life. MMP activity is increased in areas of inflammation, including periodontitis, leading to unwanted amounts of tissue destruction.

Systemic Regulators of bone Remodeling

Calcium and phosphate Balance

Calcium (Ca2+) is one of the main components of our bones. Ca2+ balance is basically maintained by two hormones: parathyroid hormone (PTH) and calcitriol (1,25-dihydroxyvitamin D). Parathyroid hormone is secreted when the level of calcium in the blood falls below the amount needed by the body's cells. It promotes the absorption of calcium by the digestive system and slows the excretion of calcium into the urine. It also stimulates osteoclasts to break down bone to release calcium into the blood. When the calcium level in the blood is adequate, the production of parathyroid hormone falls.

A third Ca2+ regulating hormone, **calcitonin**, is of minor importance in humans. It is secreted by parafollicular C cells in the thyroid gland and lowers plasma Ca2+ levels for a short time by directly inhibiting osteoclast activity, with the system quickly swinging back to a neutral position.

Hormonal Factors

Table 3 Hormonal Regulators of Bone Remodeling

	Bone resorption (osteoclast activity)	Bone formation (osteoblast activity)
Parathyroid Hormone	↑	↑ *
Vitamin D	↑	↑ *
Calcitonin	↓	-
Estrogen	↓	↓#
Growth hormone	↑	↑
Thyroid hormone	↑	↑

***PTH and Vitamin D** decreases collagen synthesis in high doses. # **Estrogen** decreases bone formation by decreasing remodeling, but formation is decreased less than resorption and bone mass increases.

Pathophysiology of Bone Remodeling

Cooper reported that systemic conditions which may provoke bone loss are currently regarded as one of the factors that affect an individual's susceptibility to periodontal disease. A few of the pathological entities wherein there is deranged skeletal metabolism/remodeling are addressed below.

Table 4 Abnormalities of Bone Remodeling in Diseased Conditions:

	Bone Resorption	Bone formation
Osteoporosis	↑↑	±↑
Glucocorticoid	↑	↓↓
Periodontitis	↑↑	↓↓
Hyperthyroidism	↑↑	↑↑
Paget disease	↑↑	↑↑
Inflammation	↑↑	±↓
Immobilization		↓↓

DISCUSSION

Bone remodeling involves tight coupling and regulation of osteoclasts and osteoblasts and is modulated by a wide variety of hormones and osteocyte products secreted in response to mechanical stimulation and microdamage. This process is often characterized by complex mechanical and biochemical signaling pathways.

Initially, bone resorption is conducted via a resorptive stimulus produced by cytokines or mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), parathyroid hormone (PTH), PTH-related protein (PTHrP), prostaglandin E2 (PGE2), and tumor necrosis factor-alpha (TNF-α). In response to a specific stimulus, preosteoclasts are recruited from the hematopoietic lineage into the area of bone resorption and differentiate into active osteoclasts. Osteoclasts possess the ruffled membrane and clear zone that ensure the resorption process remains localized beneath the osteoclast, maintaining the pH-regulating proton pump in the bone resorptive microenvironment. Resorption gradually slows and eventually ceases as the active osteoclasts are replaced with transient mononuclear cells; this is the reversal phase.

The formative phase then begins with recruitment of pre-osteoblasts (mesenchymal precursor cells) into the site. This is followed by differentiation of pre-osteoblasts into osteoblasts via the action of bone morphogenetic proteins (BMPs). In this stage, some osteoblasts are entrapped in the bone matrix and become osteocytes. Through the coupled process of bone resorption and formation, on average, an exchange of 10% of the skeleton occurs every year over an individual's lifetime. Inappropriate regulation of bone remodeling can also lead to the net bone loss seen in osteopenia and periodontitis.

CONCLUSION

With the advent of new technologies, the coupling process of bone remodeling that happens within the BMUs has been explored from various perspectives. A thorough understanding of the basic biology of bone remodeling is critical for elucidation of the molecular and cellular mechanisms underlying the pathogenesis of disorders of bone remodeling and also helps to encounter the underlying pathophysiology of several bones diseases. This knowledge will also unravel the opportunities in devising new therapeutic strategies to control bone formation and resorption based upon these novel regulatory mechanisms.

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