Chapter from the book *Topics in Osteoporosis*

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1. Introduction

Bone is a dynamic tissue in constant change; maintenance of bone mass throughout life relies on the bone remodeling process, which continually replaces old and damaged bone with new bone. This remodeling is necessary to maintain the structural integrity of the skeleton and allows the maintenance of bone volume, the repair of tissue damage and homeostasis of calcium and phosphorous metabolism. This process allows the renewal of 5% of cortical bone and trabecular 20% in a year, and although the cortical portion makes up most of the bone (75%), the metabolic activity is ten times greater in the trabecular since the relationship between surface and volume is greater in this, which is achieved by an annual renewal of 5-10% of bone volume and although this remodeling takes place throughout life, your balance is positive only during the first three decades. The skeleton is particularly dependent on mechanical information to guide the resident cell population towards adaptation, maintenance and repair; a wide range of cell types depend on mechanically induced signals to enable appropriate physiological responses. The bone remodeling has two main phases: a resorption phase, consisting of the removal of old bone by osteoclasts, and a later phase of formation of new bone by osteoblasts that replaces the tissue previously resorbed. While osteoclasts are derived from hematopoietic precursor cells and degrade the bone matrix, osteoblasts originate from mesenchymal stem cells, they deposit a collagenous bone matrix and orchestrate its mineralization. While the interaction of bone cells with their mechanical environment is complex, an understanding of mechanical regulation of bone signaling is crucial to understanding bone physiology, the etiology of bone diseases such as osteoporosis, and to the development of interventions to improve bone strength. The clinical importance of bone formation has stimulated a lot of research aimed at understanding its mechanism. Much knowledge has been gained in the recent years, especially in relation with the signaling pathways controlling osteoblast differentiation. The purpose of this chapter is to review current knowledge on biochemical and
physiological mechanisms of remodeling bone, with particular attention to the role in the cell involved, the process, regulation signals into the control and pathophysiology of bone remodeling (diseases).

2. Cells involved in bone remodeling

Two bone cell lineages have been identified: cells of the osteoblast lineage (osteoblasts, osteocytes and bone-lining cells) and bone resorbing cells (osteoclasts) that together with their precursor cells and associated cells (e.g. endothelial cells, nerve cells) are organized in specialized units called bone multi cellular units (BMU). The main function of the BMU is to mediate a bone “rejuvenation” mechanism called “bone remodeling”. Bone remodeling maintains the integrity of the skeleton by removing old bone of high mineral density and high prevalence of fatigue micro-fractures through repetitive cycles of bone resorption and bone formation [1]. This is a direct and crucial interaction that has been well established in vivo. Once osteoblasts and osteoclasts are fully differentiated, there is a less direct relationship [2]. Despite the know close physiological interactions of the two main cellular systems in bone, there are effectively separate and distinct origins of osteoblast (hematopoietic cell origin) and stromal/osteoblast linages from the developing fetus onward in mammalian development; circulating osteogenic precursor cells are blood-borne cells that express a variety of osteoblastic markers and are able to form bone in vivo. Strong evidence suggests that cells are derived from bone marrow and are of hematopoietic origin [3].

2.1. Osteoblast

Osteoblasts derive from mesenchymal precursor cells, which also originate, chondrocytes (cartilage), adipocytes (bone marrow stroma), fibroblasts (periosteum), and adventitial reticular cells (bone marrow stroma). Although the claim that bone marrow stromal cell can also give raise chondrocytes, myoblasts, adipocytes and tendon cells, depending on the transcription factors that regulate the pathway [4]. There are four stages that have been identified in osteoblast differentiation: the preosteoblast, osteoblast, osteocyte and bone-lining cell that histologically these cells stain positively for alkaline phosphatase, however, only mature osteoblasts have the ability to produce mineralized tissue [5], and can be identified by their cuboidal morphology and strong alkaline phosphatase positivity. The master gene that encodes for a protein involved in the osteogenic differentiation process from mesenchymal precursors is the nuclear transcriptional factor Runx-2 (Runt related transcription factor 2, cbfa-1) (Figure 1) [6].

The osteoblast resides along the bone surface at sites of active bone formation. They secrete type 1 collagen, the basic building block of bone; non-collagenous proteins including osteocalcin and alkaline phosphatase, which is essential for mineral deposition [7]. The principal function of the osteoblast is bone formation and these occur via two distinct mechanisms: the intramembranous ossification (flat bones of the skull and most of the clavicle) and the endochondral ossification, which produces most bones, involves the transformation of mesenchyme
into a cartilage model that resembles the shape of the bone [8]. They are also responsible for the mineralization, although the exact mechanism by which mineralization occurs remains unclear [9]. Mature osteoblasts have one of three fates: they undergo apoptosis, differentiate further into osteocytes or become quiescent lining cells. Approximately 50 to 70% of osteoblasts undergo apoptosis [10].

2.2. Osteocyte

Osteocytes are non-proliferative, terminally differentiated cells of the osteoblast lineage, how osteoblasts transform into osteocytes is dependent on the mode of ossification (Figure 1). They reside both in the mineralized bone matrix and in newly formed osteoid, locked inside small lacuna spaces in the hard substance of bone are smaller than osteoblasts and have lost many of their cytoplasmic organelles [11-13]. They compose over 90–95% of all bone cells in the adult skeleton and are thought to respond to mechanical strain to send signals of resorption or formation, due to their distribution throughout the bone matrix and extensive interconnectivity, osteocytes are thought to be one if not the major bone cell type responsible for sensing mechanical strain and orchestrating signals of resorption and formation. Evidence suggests that the primary function of the osteocyte relates to the determination and maintenance of bone structure. Osteocytes are mechanosensors capable of transducing musculoskeletal derived mechanical input into biological output [14], the osteocyte appears to be capable of

Figure 1. Osteoblasts derive from Mesenchymal Stem Cells. Osteoclasts derive from by the fusion of mononuclear progenitors of the monocyte/macrophage family, and Osteocytes are non-proliferative differentiated cells of the osteoblast lineage.
relating the intensity of strain signals and the distribution of the strain throughout the whole bone into signals to regulate [15]. Microdamage in the bone matrix has been shown to initiate bone remodeling, the osteocytes located near these sites undergo apoptosis correlated with increased bone remodeling due to enhanced RANKL production and an increase in osteoclast formation [16], and the osteocytes may be the major source of RANKL during bone remodeling [17-19]. For some time it has been estimated that the average life of this cell would be 25 years. The percentage of dead osteocytes increases with age senescence, being from 1% to 75% rise in the eighth decade [20,21].

2.3. Osteoclast

Osteoclasts, which are the only cells capable of resorbing bone, are multinucleated giant cells formed from by the fusion of mononuclear progenitors of the monocyte/macrophage family in a process termed osteoclastogenesis (Figure 1) [22], they are located on endosteal surfaces within the Haversian system and on the periosteal surface beneath the periosteum, in the bone has only two to three per μm $^3$ [23]. Osteoclasts are terminally differentiated myeloid cells that are uniquely adapted to remove mineralized bone matrix. These cells have distinct morphological and phenotypic characteristics that are routinely used to identify them, including multinuclearity and expression of tartrate-resistant acid phosphatase and the calcitonin receptor. Osteoclast differentiation is supported by cells of the osteoblast lineage that express membrane-bound receptor activator (RANK) of RANKL (NF-kB ligand) and macrophage-colony stimulating factor (M-CSF) [22]; this process is also regulated by a secreted decoy receptor of RANKL, osteoprotegerin (OPG), which functions as a paracrine inhibitor of osteoclast formation [24]. The balance between OPG and RANKL regulates bone resorption and formation and one imbalance of the RANKL/OPG system have been implicated in the pathogenesis of various primary and secondary bone malignancies [25]. In the motile state the osteoclast migrate from the bone marrow to their resorptive site and in the resorptive phase they exert their bone resorbing function, in each state the osteoclast display morphological differences [26], the motile osteoclasts are flattened, non-polarised cells and they are characterised by the presence of membrane protrusions (lamellipodia), and podosome. Upon reaching the resorptive site, osteoclasts become polarised through cytoskeletal reorganization, results in the formation of a ruffled border, sealing zone, functional secretory domain and basolateral membrane. The sealing zone is an osteoclast specific structure, which separates the acidic resorptive environment from the rest of the cell, forming an organelle free area [27].

2.4. Bone-lining cells

The bone lining cells constitute a subpopulation of the osteoblast family. Bone lining cells were characterized by their long, slender, and flattened appearance; and their association with the bone surface at sites where a thin no mineralized collagen layer was present [28]. Although not being osteoblasts in the sense that they produce an osteoid layer, belong to the same lineage as osteoblasts for the following reasons: they are alkaline phosphatase positive, respond to PTH, and are associated with the bone surface. The bone lining cells contained a low level of labeled osteocalcin, and they have electron-dense vacuoles containing crossbanded collagen
fibers in the cytoplasm [28]. It has been proposed that bone lining cells play a role in bone remodeling by preventing the inappropriate interaction of osteoclast precursors with the bone surface. It is thought that the signals that initiate osteoclast formation may stimulate the bone lining cells to prepare for bone resorption, through the actions of collagenase which digests a thin layer of non-mineralized bone, revealing the mineralized matrix underneath [29,30]. The bone lining cells migrate to form a canopy over the remodeling area, particularly at sites adjacent to osteoclasts, creating a microenvironment (in phagocytosis of collagen at the bone surface) for the coupling required during bone remodeling. It has been proposed that the bone lining cells are responsible for the cell to cell interactions between RANKL and RANK receptor on osteoclast precursors [31].

3. Bone remodeling: The process

The normal bone remodeling is a process that couples bone resorption and bone formation, it occurs in discrete locations and involves a group of different kinds of cells and takes 2 to 5 years for an area on the bone surface to complete one bone remodeling cycle [32]. The bone tissue is morphologically and physiologically separated from the marrow by bone lining cell; the process of cancellous bone remodeling occurs on the surface of trabeculae at the boundary between bone and marrow. In normal bone length of the remodeling is about 200 days, with the majority of that time (approx. 150 days) devoted to bone formation [33]. The bone remodeling takes place in the BMU and the skeleton contains millions which comprises the next: osteoclasts that resorbing the bone, the osteoblasts that replacing the bone, the osteocytes within the bone matrix, the bone lining cells that covering the bone surface and the capillary blood supply. All BMU are in different stages, and the life span of individual cells in a BMU is much shorter than that of a BMU [31,35,36]. Mechanical stress in the bone can be sensed by osteocytes that can signal giving to lining cells to form a new BMU at cortical or cancellous surfaces and estimates that the duration is 2-8 months [12]. The bone remodeling follows coordination of distinct and sequential phases of this process, (Figure 2):

*Activation Phase*- The first stage of bone remodeling involves detection of an initiating remodeling signal, the activation is a continuing process that occurs at the cutting edge of the BMU, and this signal can take several forms as a direct mechanical strain on the bone that results in structural damage or hormone (e.g. estrogen or PTH) action on bone cells in response to more systemic changes in homeostasis [32]. Conceivably, osteocyte apoptosis and possible release of osteotropic growth factors and cytokines could be attractants for blood vessels, which would then subsequently initiate the formation of a resorptive of the bone remodeling compartment which are a prerequisite for osteogenesis, including bone development, fracture healing, and cortical bone remodeling that support recruitment of osteoblast progenitors to bone remodeling sites, thus highlight a link between activation of bone remodeling on the cancellous bone surfaces and activation of neighbouring bone marrow events [12,34,36,37]. The mechanical environment to which bone cells are exposed is a dynamic milieu of biophysical stimuli that includes strain, stress, shear, pressure, fluid flow, streaming potentials and acceleration. While ultimately it may not be possible to separate specific effects of each of these factors, it is clear
that several of these parameters independently have the ability to regulate cellular responses and influence remodeling events within bone. Furthermore, components of these specific factors (such as magnitude, frequency, and strain rate) also affect the cellular response [38].

Figure 2. Schematic presentation of trabecular and cortical bone remodeling by BMU. In trabecular, the osteoclast create Howship’s lacunas that are refilled by osteoblast, and in the cortical bone, the osteoclast erode bone tissue and are followed by osteoblast that refill the gap with new bone.

The osteocyte, which is uniquely situated in cortical bone to sense mechanical strain and load generated factors (e.g., fluid flow, streaming and pressure) through a connected network of sister cells contributes to the perception of and response to loading and unloading [12], this canalicular network responds to unloading, or a decrease in mechanical signals, with upregulation of the proteins sclerostin and RANKL that control bone remodeling at multiple levels. The long osteocytic processes are able to pass information between cells separated by hard tissue [16,19]. Osteoblast lineage cells and bone marrow stromal cells (BMSCs) are thought to be the major cell types that express RANKL in support of osteoclastogenesis [39,40]; however the actual major source of RANKL in vivo is the osteocyte [12].

Resorption Phase- In this phase, the formation and activity of osteoclasts is controlled by cells of the osteoblast lineage that recruit osteoclast precursors to the remodeling site with the expression of the master osteoclastogenesis cytokines, CSF-1, RANKL, and OPG, is also modulated in response to PTH [32,45,46]. Remodeling is initiated by osteoclastic resorption, which erodes a resorption lacuna, they attach to the bone surface, sealing a resorbing compartment that they acidify by secreting H⁺ ions, facilitating dissolution of the bone mineral and thereby exposing the organic matrix to proteolytic enzymes that degrade it, during resorption the bone matrix and bone mineral is digested. Some fragments can be used as biochemical markers for overall bone resorption [43]. The depth of which varies between 60-40 μm in young and older individuals, and the resorption period has a median duration of 30–40 days [45]. In cortical bone, the BMUs proceed by osteonal tunnelling, during which osteoclasts excavate a canal that is refilled by osteoblasts, the so-formed Haversian systems are 100–200 μm wide and may become as long as 10 mm; their
orientation is along the main loading direction trabecular, by contrast, are eroded as grooves along the bone surface with a depth of 60–70 μm (Figure 2), [36].

Reversal Phase- This phase lasts ~9 days, occurs after the maximum eroded depth has been achieved. In the reversal period the osteoclasts undergo apoptosis whilst osteoblasts are recruited and begin to differentiate [44], therefore the reversal phase is a transition from osteoclast to osteoblast activity [35]. After withdrawal of the osteoclast from the resorption pit, bone-lining cells enter the lacuna and clean its bottom from bone matrix leftovers. This cleaning proves to be a prerequisite for the subsequent deposition of a first layer of proteins (collagenous) in the resorption pits and form a cement line (glycoprotein) that helps in attaching osteoblasts (Figure 2), [28,41].

Formation Phase- The bone formation by the osteoblasts lasts the longest, and is slower than bone resorption, involves new bone formation and mineralization. It was proposed that the coupling molecules were stored in the bone matrix and liberated during bone resorption. TGF-β appears to be a key signal for recruitment of mesenchymal stem cells to sites of bone resorption and osteoclasts produce the coupling factors [32,45], once mesenchymal stem cells or early osteoblast progenitors have returned to the resorption lacunae, they differentiate [28, 34,46] and the proliferating osteoblasts forming multilayers of cells. Several genes associated with formation of the extracellular matrix (Type I collagen, fibronectin, and TGF-β) are actively expressed and then gradually decline being maintained at a low basal level during subsequent stages of osteoblast differentiation. Collagen type I is the primary organic component of bone and accumulation contributes, in part, to the cessation of cell growth. When proliferation ceases, proteins associated with bone cell phenotype are detected, e.g. alkaline phosphatase enzyme, osteocalcin [7,47]. Bone matrix is built up of type I collagen (88%) and the remaining 10% is composed of a large number of non-collagenous proteins (e.g. osteocalcin, osteonectin, bone sialoprotein and various proteoglycans) and lipids and glycosaminoglycans represent 1–2% [48]. For bone to assume its final form, hydroxylapatite is incorporated into this newly deposited osteoid [47,49]. The extracellular matrix undergoes a series of modifications in composition and organization that renders it competent for mineralization that begins ~15 days after osteoid has been formed, and non-collagenous proteins participate in the process of matrix maturation, mineralization and may regulate the functional activity of bone cells. With the onset of mineralization, several other bone expressed genes are induced to maximal levels (bone sialoprotein, osteopontin and osteocalcin) [32,47]. The composition of bone is approximately 10% cells, 60% mineral crystals (crystalline hydroxyapatite), and 30% organic matrix [48]. When an equal quantity of resorbed bone has been replaced, the remodeling cycle concludes (Figure 2).

Termination Phase- The termination signals are largely unknown, and include the terminal differentiation of the osteoblast. The role of osteocytes is emerging [12,32]. The cells then gradually flatten as they slow production, and finally they become quiescent lining cells. Some of the osteoblast differentiate into osteocytes and remain in the matrix [12]. The osteocytes may secrete inhibitory factors that slow the rate of bone formation as the resorbed cavity is nearly filled. Bone remodeling is mediated by a balance of osteoblast and osteoclast cell activity, which together, maintain bone mass and mineral homeostasis. Both decreased bone formation and
increased bone resorption may result in bone loss. Therefore, the stimulation of bone formation may be another important factor for the prevention and treatment of bone loss (Figure 2).

4. Regulation signals into the control of bone remodeling

4.1. Systemic regulation of bone remodeling

The process of bone remodeling is essential for adult bone homeostasis. This control involves a complex mechanism compound by numerous local and systemic factors, and their expression and release is controlled finely. The main factor that affects normal bone remodeling is the regulation of osteoblasts and osteoclasts. Local and systemic factors can affect bone remodeling by directly or indirectly targeting mature cells and their respective progenitor cells. The metabolic functions of the bone are mediated by two major calcium-regulating hormones, parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D (Table 1) [50].

<table>
<thead>
<tr>
<th>Bone reabsorption (osteoclast activity)</th>
<th>Bone Formation (osteoblast activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>↑</td>
</tr>
<tr>
<td>1,25(OH)2 Vitamin D</td>
<td>↑</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>↓</td>
</tr>
<tr>
<td>Estrogen</td>
<td>↓</td>
</tr>
<tr>
<td>Growth hormone/IGF</td>
<td>↑</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>↑</td>
</tr>
</tbody>
</table>

? = Effects are not Known

* PTH and vitamin D decrease collagen synthesis in high doses.

# Estrogen decreases bone formation by decreasing remodeling, but formation is decreased less than resorption and bone mass increases.


Table 1. Local and systemic regulation of bone remodeling.

PTH is a stimulator of bone resorption and 1,25-Dihydroxy vitamin D has its greatest effect on intestinal calcium and phosphate absorption, but it may also have direct effects on bone and other tissues. It is probably critical for the differentiation of both osteoblasts and osteoclasts and can stimulate bone resorption and formation under some experimental conditions. A third hormone, calcitonin (Table 1), in contrast to PTH and 1,25(OH)2 D3, both of which increase calcium release from the mineralized matrix, calcitonin is an inhibitor of osteoclast activity. It is a potent inhibitor of bone resorption and is used clinically in the treatment of bone diseases. Other systemic hormones are keys in regulating bone remodeling, such as: Growth hormone...
acting through both systemic and local insulin-like growth factor (IGF) production, can stimulate bone formation and resorption. Glucocorticoids are necessary for bone cell differentiation during development. Indirect effects of glucocorticoids on calcium absorption and sex hormone production may, however, increase bone resorption (Table 1). On the other hand, probably the most important systemic hormone in maintaining normal bone turnover is estrogen. Estrogen deficiency leads to an increase in bone remodeling in which resorption overcome formation and bone mass decreases (Table 1). The increase in bone remodeling and in bone resorption in the estrogen deficient state is associated with an increase in bone formation at the tissue level [51]. Therefore, sex steroid deficiency is associated with a defect in bone formation. Based on the available evidence, there are currently at least three key mechanisms by which estrogen deficiency may lead to a relative deficit in bone formation through direct effects on osteoblasts: increased apoptosis, increased oxidative stress, and an increase in NF-κB activity (Figure 3). In addition, estrogen inhibits the activation of bone remodeling, and this effect is most likely mediated via the osteocyte [52].

4.2. Parathyroid hormone (TH) and PTHrP signals

The parathyroid hormone (PTH) increases bone formation in bone diseases. The anabolic effects of PTH on bone formation are mediated through the PTH/PTH-related peptide (PTHrP) receptor-dependent mechanisms that generate multiple G protein-dependent signals (Table 1). PTH mediated cyclic AMP/protein kinase phosphorylates the osteoblast transcription factor Runx2, which in turn upregulates the expression of osteoblast genes. Intermittent PTH also activates ERK1/2-mitogen-activated protein kinase (MAPK) Erk1/2 and phosphatidylinositol phosphate (PI3K) signaling, resulting in increased osteoblastogenesis and osteoblast survival (Figure 3) [53]. PTH induces the synthesis of IGF-I that works with PTH in osteoblasts to stimulate osteoblast proliferation and differentiation as well as indirectly regulates osteoclast activity [54,55]. Also, PTH was inferred to interact with various local signaling molecules, including insulin-like growth factors and Wnt antagonist sclerostin (SOST) [55-57]. It was recently shown that, in addition to reducing SOST, PTH reduces Dkk1 expression and thereby increases Wnt signaling, which contributes to the anabolic effect of PTH in bone [58]. This does not exclude the possibility that PTH receptor signaling may increase bone mass and bone remodeling by affecting Wnt signaling in other cell types. Recent data indicate that the activation of the PTH receptor in T lymphocytes plays a role in PTH-induced bone formation and bone mass by promoting the production of Wnt10b by these cells [59]. These observations and the finding that PTH signaling also acts by phosphorylating the Wnt coreceptor LRP6 and β-catenin indicate that direct and indirect crosstalks between PTH and Wnt signaling are important mechanisms regulating bone formation.

4.3. Wnt and Wnt antagonists

Genetic studies in human and animal models suggest that the canonical Wnt/β-catenin pathway (Table 2), together with BMP signaling and key transcription factor RUNX2(CBFA1/AML3), has an key role in skeletal development, osteoblast differentiation and bone formation [60,61]. Wnt/β-catenin signaling plays a significant role in promoting mesenchymal commit-
ment to the osteoblastic lineage during the embryonic bone development. The canonical Wnt/β-catenin signaling activity is promoted in the forming osteoblast, and this activity promotes osteoblast differentiation during endochondral bone formation, and the skeletal development is affected and the osteoblast differentiation is reduced when Wnt/β-catenin signaling is interrupted in the mesenchyme (Figure 3) [62]. The in vivo stimulation of the Wnt10b signaling cascade in the FABP4 promoter-Wnt10b transgenic mice led to a significantly higher bone mass because of the stimulation of osteoblastogenesis and the inhibition of adipogenesis. In addition, the Wnt10b−/−mice had decreased trabecular bone and serum osteocalcin [63]. Recent advances have been made in our understanding of the role of Wnt proteins in bone cell biology. It was found that, in addition to Wnt10b [63], several other Wnt proteins (Wnt6a, Wnt10a) influence the differentiation of mesenchymal precursors into osteoblasts or adipocytes, and thereby control bone mass [64]. The Wnt signal is modulated by various antagonists, including secreted factors, transmembrane modulators, and intracellular signals. Dickkopf family members (Dkk1 and Dkk2) and secreted frizzled related proteins (Sfrps) are families of extracellular proteins that negatively modulate canonical Wnt signalling [60].

4.4. Transforming growth factor-β

The transforming growth factor-β (TGF-β) signaling pathway, is known to control bone remodeling and maintenance. However, TGF-β exerts both positive and negative effects on bone cells, causing bone loss or bone gain in mice. There are three isoforms of TGF-β, namely, TGF-β1, TGF-β2, and TGF-β3. TGF-β1, known as the most abundant TGF-β isoform in the bone tissue, has been intensively studied during bone remodeling [65]. A study on the mechanism of TGF-β for osteoblast regulation has indicated that TGF-β1 stimulates bone matrix apposition and osteoblast proliferation in vitro. Additional research revealed that although TGF-β1 stimulates the early differentiation of osteoblast cells, this factor suppresses the late stage of osteoblast differentiation. These signals are transduced together by the activation of R-smads and Cosmads as well as through the mitogen-activated protein kinase (MAPK) pathway (Table 2). A cross talk exists between the TGF-β signal and the parathyroid hormone (PTH) in the regulation of osteoblastogenesis [66]. PTH stimulates the production of TGF-β1 and TGF-β2 in the osteoblast. In addition to regulating the osteoblastic bone formation, TGF-β1 has a key role in regulating bone remodeling by connecting bone formation and bone resorption (Figure 3). TGF-β proteins are present in their latent form in the bone matrix, and osteoclasts can release, as well as activate, TGF-β from the bone matrix via osteoclastic bone resorption. The released TGF-β may in turn stimulate the osteoblastic bone formation [45].

4.5. Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs), they are so named for their osteoinductive properties, and regulate differentiation of mesenchymal cells into components of bone, cartilage or adipose tissue. TGF-β/BMP ligand signal is mediated by serine/threonine protein kinases (receptor types 1 and 2) and a family of receptor substrates (the Smad proteins) that move into the nucleus. BMP signaling is important for skeletal development and maintenance of bone mass through activation of BMP type 1A (BMPR1A) and type 1B receptors that control
osteoblast function and bone remodeling (Table 2) [67]. Notably, BMPR1A in osteoblasts negatively regulates bone mass and Wnt/β-catenin signaling through upregulation of the Wnt inhibitors Sost and Dkk1 in mice [68]. Also, BMPs promote osteoblastogenesis through the Smad and MAPK pathways, which upregulates the expression of Runx2 and Osx, and thus stimulate the bone formation (Figure 3). BMP signaling is modulated by multiple agonists and antagonists acting at the extracellular level, which are also important for bone remodeling and may be potential therapeutic targets [69]. It was found that the Wnt-induced secreted protein 1 (WISP-1/CCN4) enhances BMP2-induced signaling (Smad-1/5/8 phosphorylation and activation), resulting in increased osteogenic differentiation and bone mass in mice.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Receptors</th>
<th>Activated pathways</th>
<th>Target Cells</th>
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<tr>
<td>PTH</td>
<td>PTH/PTHrP</td>
<td>cAMP/PCA, PKC, PI3K/Akt, Wnt</td>
<td>Osteoblasts</td>
</tr>
<tr>
<td>Wnt3a</td>
<td>LRPS/LRP6/Frizzled</td>
<td>Wnt, PI3K/Akt</td>
<td>Osteoblasts</td>
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<tr>
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<td>TGF-B type II</td>
<td>cAMP/PCA, PKC, PI3K/Akt, Wnt</td>
<td>Osteoblasts/osteoclasts</td>
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<tr>
<td>BMP</td>
<td>BMPR1A</td>
<td>Wnt</td>
<td>Osteoblasts/osteoclasts</td>
</tr>
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<td>Ephrins</td>
<td>Eph</td>
<td>c-Fos-NFATc1</td>
<td>Osteoblasts/osteoclasts</td>
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<tr>
<td>EGFR</td>
<td>ERBB1-4</td>
<td>Ras-Raf-Map-Kinase</td>
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<td>FGF2</td>
<td>FGFR1/2</td>
<td>Erk1/2, PKCa, Wnt</td>
<td>Osteoblasts</td>
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<td>IGF-1/IGFBP2</td>
<td>IGFR</td>
<td>Akt, Wnt</td>
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<td>Brain derived serotonin (BDS)</td>
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<td>Semaphorin 4D</td>
<td>Plexin-B1</td>
<td>RhoA/IGF1</td>
<td>Osteoblasts/osteoclasts</td>
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</table>

Table 2. Signaling pathways affecting bone cells and bone remodeling.

### 4.6. Eph and Ephrin interactions

The interactions between Eph and Ephrin play important roles in bone cell differentiation and patterning by exerting effects on osteoblast and osteoclast differentiation, resulting in the
coupling of bone resorption and bone formation. Eph receptors are tyrosine kinase receptors activated by ligands called ephrins (Eph receptor interacting proteins). Both Ephs and ephrins are divided into two A and B groups [70]. To date, ephrinB2, a transmembrane protein expressed on osteoclasts, and its engagement with its receptor, EphB4, on osteoblasts, lead to bi-directional signaling between these cells; this is one of the cell-cell contact mechanisms that mediate crosstalk between these cells. EphrinB2 (as reverse signaling), located on the surface of osteoclast precursors, suppresses osteoclast precursor differentiation by inhibiting the osteoclastogenic c-Fos-NFATc1 cascade (Table 2) [71]. In addition, the signaling mediated by EphB4 (as forward signaling) located on the surface of osteoblast enhances the osteogenic differentiation. Ephrin B1 induces osteoblast differentiation by transactivating the nuclear location of transcriptional coactivator with PDZ-binding motif (TAZ), a co-activating protein of Runx2. TAZ, together with Runx2, induces osteoblast-related gene expression [72]. The functional role of the EphrinA2–EphA2 complex differs significantly in its interactions compared with the EphrinB2–EphB4 complex. Both the reversed signaling EphrinA2 and forward signaling EphA2 stimulate osteoclast differentiation, but EphA2 has a negative role in bone formation by inhibiting osteoblast differentiation through the regulation of RhoA activity (Figure 3) [71].

Figure 3. Key signaling pathways for regulating osteoblastogenesis in bone remodeling. BMPs/TGF-β, Wnt, intermittent PTH and Wnt5a-Ror2 stimulate osteoblast differentiation. Eph–Ephrin and RANKL-RANK signal mediate osteoblast–osteoclast interaction. TGF-β1 secretion mediated by osteoclastic bone resorption induces BMSC migration and bone formation. Leptin–brainstem-derived serotonin-sympathetic nervous system and Sema4D pathway suppresses osteoblast proliferation, whereas gut-derived serotonin inhibits osteoblast proliferation.
4.7. Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR) is a glycoprotein on the cell surface of a variety of cell types and is characterized by its ligand-dependent tyrosine kinase activity. After ligand binding to the extracellular domain, the EGFRs are activated by homo- or heterodimerization with auto- and transphosphorylation on tyrosine residues at the intracellular domain, and then a variety of signaling pathways, such as Ras-Raf-MAP-kinase and PI-3- kinase-Akt, are activated to influence cell behaviors, such as proliferation, differentiation, apoptosis, and migration (Table 2) [73]. In recent years, several experiments indicate that the epidermal growth factor receptor (EGFR) system plays important roles in skeletal biology and pathology. This network, including a family of seven growth factors – the EGFR ligands – and the related tyrosine kinase receptors EGFR (ERBB1), ERBB2, ERBB3 and ERBB4, regulates aspects such as proliferation and differentiation of osteoblasts, chondrocytes and osteoclasts, parathyroid hormone-mediated bone formation and cancer metastases in bone (Figure 3) [74]. In addition, EGFR signaling affects osteoclasts, albeit this could be an indirect effect mediated by inhibition of OPG expression and increased RANKL expression by osteoblasts [74]. It was recently found that decreasing EGFR expression in pre-osteoblasts and osteoblasts in mice results in decreased trabecular and cortical bone mass as a consequence of reduced osteoblastogenesis and increased bone resorption [48].

4.8. Fibroblast Growth Factors (FGFs)

Signaling induced by Fibroblast Growth Factors (FGFs) regulate osteoblastogenesis and bone formation. Multiple signaling pathways activated by FGF receptors 1 and 2 control osteoblast proliferation, differentiation, and survival (Table 2). FGFs bind to high affinity FGF receptors (FGFR), leading to FGFR dimerization, phosphorylation of intrinsic tyrosine residues and activation of several signal transduction pathways [75]. Recent studies provided some insights into specific signaling pathways induced by FGF/FGFR signaling that control osteoblasts. Activation of ERK1/2 signaling by FGF was found to be essential for promoting cell proliferation in osteoblast precursor cells [76]. In addition, activation of ERK1/2 is involved in FGFR2-mediated osteoblast differentiation. Activation of ERK-MAP kinase by activating FGFR2 mutations results in increased transcriptional activity of Runx2, an essential transcription factor involved in osteoblastogenesis, and increased osteogenic marker gene expression (Figure 3) [77]. Recent data indicate that FGF2 stimulates osteoblast differentiation and bone formation in part by activating Wnt signaling suggesting that Wnt signaling may mediate, at least in part, the positive effect of FGF/FGFR signaling on bone formation in mice [78]. Besides Wnt signaling, FGF/FGFR signaling interacts with other pathways. One interaction involves a negative regulation of the BMP antagonist Noggin by FGF2 during skull development [79]. Another interaction involves the upregulation of the BMP2 gene by endogenous FGF/FGFR signaling in calvarial osteoblasts. In vivo, FGF2 treatment of developing bone fronts promotes BMP2 gene expression through the modulation of Runx2 expression [80]. These studies support a positive role of FGF and BMP signaling crosstalks on bone formation.
4.9. Insulin-like growth factor-I

The Insulin-like growth factor-I (IGF-I) signaling through its type 1 receptor generates a complex signaling pathway that stimulates cell proliferation, function, and survival in osteoblasts (Table 2) [81]. Accordingly, mice lacking functional IGF-I exhibit severe deficiency in bone formation and a 60% deficit in peak bone mineral density (BMD) [82]. IGF-I can act in an endocrine, paracrine or autocrine manner and is regulated by a family of six IGF binding proteins (IGFBPs). The IGFBPs, have received considerable attention as regulators of IGF actions. The IGFBPs have been reported to have stimulatory or inhibitory actions on the IGFs in bone, and recent experiments have provided evidence that some of IGFBPs function independently of IGF to increase parameters of bone formation. The IGFBPs are often found bound to IGF-I in the circulation or complexed with IGF-I in osteoblasts. IGFBP-3 and -5 are known stimulators of IGF-I actions, whereas IGFBP-1, -2, -4 and -6 are known inhibitors of IGF-I action in bone. Once IGF-I binds to its receptor (type 1 IGF receptor) it initiates a complex signaling pathway including the phosphoinositol 3-kinase (PI3-K)/3-PI-dependent kinase (PDK)-1/Akt pathway and the Ras/Raf/mitogen-activated protein (MAP) kinase pathway which stimulate cell function and/or survival (Figure 3) [83]. Recent findings indicate that many of the IGFBPs and specific proteins in the IGF-I signaling pathways are also potent anabolic factors in regulating osteoblast function and may serve as potential targets to stimulate osteoblast function and bone formation locally.

4.10. Leptin–serotonin system pathway regulation of bone formation through gut-derived serotonin

A new regulation mode of osteoblastic bone formation controlled by leptin-serotonin (BDS)-sympathetic nervous system pathway has emerged in recent years. Leptin is a hormone produced by adipocytes that, besides its function in regulating body weight and gonadal function, can also act as an inhibitor of bone formation (Figure 3) [84]. Latest data indicates that these leptin functions require brainstem-derived serotonin [85]. Serotonin is a bioamine produced by neurons of the brainstem (brainstem-derived serotonin, BDS) and enterochromaffin cells of the duodenum (gut-derived serotonin, GDS). BDS acts as a neurotransmitter, while GDS as an autocrine/paracrine signal that regulates mammary gland biogenesis, liver regeneration, and gastrointestinal tract motility [86]. There are two Tph genes that catalyze the rate-limiting step in serotonin biosynthesis: Tph1 expressed mostly, but not only, in enterochromaffin cells of the gut and is responsible for the production of peripheral serotonin [86]. Tph2 is expressed exclusively in raphe neurons of the brainstem and is responsible for the production of serotonin in the brain [87]. Leptin inhibits BDS synthesis by decreasing the expression of Tph2, a major enzyme involved in serotonin synthesis in brain [85]. In addition, other data indicate, the key role of GDS in regulating bone formation as well as the relationship between GDS, Lrp5, and bone remodeling. Lrp5 controls bone formation by inhibiting GDS synthesis in the duodenum, and GDS directly acts on the osteoblast cells to inhibit osteoblast proliferation and suppress bone formation (Table 2) [88]. However, recent data to argue that Lrp5 affect bone mass mainly through local Wnt signaling pathway, and that the experiments
did not support the Lrp5-GDS-osteoblast model because they found that there was no relevance between GDS and bone mass in their mouse model system [89].

4.11. New signals in bone remodeling

More recently, other signaling pathways that link regulation of the osteoclasts and osteoblasts have been identified. Osteoblast-lineage cells expressed Wnt5a, whereas osteoclast precursors expressed Ror2. Connection between these two cells leads to Wnt5a-Ror2 signaling between osteoblast-lineage cells and osteoclast precursors enhanced osteoclastogenesis, through increased RANK expression mediated by JNK signaling. A soluble form of Ror2 acted as a decoy receptor of Wnt5a and abrogated bone destruction in the mouse model, suggesting that the Wnt5a-Ror2 pathway is crucial for osteoclastogenesis in physiological and pathological environments and may represent a therapeutic target for bone diseases (Figure 3) [90]. Finally, a recent study reported that semaphorin 4D (Sema4D), previously shown to be an axon guidance molecule, expressed by osteoclasts and which potently inhibits bone formation [91]. Several studies have suggested that axon-guidance molecules, such as the semaphorins and ephrins, are involved in the cell-cell communication that occurs between osteoclasts and osteoblasts. The Binding of Sema4D to its receptor Plexin-B1 in osteoblasts resulted in the activation of the small GTPase RhoA, which inhibits bone formation by suppressing insulin-like growth factor-1 IGF-1 signaling and by modulating osteoblast motility. Notably, the suppression of Sema4D using a specific antibody was found to markedly prevent bone loss in a model of postmenopausal osteoporosis (Table 2) [91]. This finding identifies a new link between osteoclasts and osteoblast signaling, and suggests that suppression of the Sema4D-Plexin-B1-RhoA signaling axis may provide a new therapeutic target for reducing bone loss and development of bone-increasing drugs.

5. Pathophysiology of bone remodeling (diseases)

Several lines of evidence have established that the cells that remodel the skeleton under physiological conditions are the same cells that mediate these processes in pathologic states. Mature bone consists of: an organic matrix (osteoid) composed mainly of type 1 collagen formed by osteoblasts; a mineral phase which contains the bulk of the body’s reserve of calcium and phosphorus in crystalline form (hydroxyapatite) and deposited in close relation to the collagen fibers; bone cells; and a blood supply with sufficient levels of calcium and phosphate to mineralize the osteoid matrix. Bone turnover and remodeling occurs throughout life and involves the two-coupled processes of bone formation by osteoblasts and bone resorption by osteoclasts and perhaps osteolytic osteocytes. Abnormalities of bone remodeling can produce a variety of skeletal disorders (Table 3). The metabolic bone diseases may reflect disturbances in the organic matrix, the mineral phase, the cellular processes of remodeling, and the endocrine, nutritional, and other factors that regulate skeletal and mineral homeostasis. These disorders may be hereditary or acquired and usually affect the entire bony skeleton. The acquired metabolic bone diseases are the more common and include: osteoporosis, osteoma-
lacia, the skeletal changes of hyperparathyroidism and chronic renal failure (renal osteodystrophy), and Paget’s disease [48,50].

5.1. Osteoporosis

Osteoporosis is a common disease of bone remodeling characterized by low bone mass and defects in the microarchitecture of bone tissue; it causes bone fragility and an increased vulnerability to fractures. The loss of bone mass and strength can be contributed to by (a) failure to reach an optimal peak bone mass as a young adult, (b) excessive resorption of bone after peak mass has been achieved, or (c) an impaired bone formation response during remodeling. Osteoporosis, is traditionally classified into primary and secondary types. Primary osteoporosis is the most common metabolic disorder of the skeleton and has been divided into two subtypes: type I osteoporosis and type II osteoporosis, on the basis of possible differences in etiology. Type I osteoporosis or postmenopausal osteoporosis is a common bone disorder in postmenopausal women and is caused primarily by estrogen deficiency resulting from menopause, whereas type II osteoporosis or age-related osteoporosis is associated primarily with aging in both women and men (Table 3). In contrast, secondary osteoporosis refers to bone disorders that are secondary complications of various other medical conditions, consequences of changes in physical activity, or adverse results of therapeutic interventions for certain disorders [92].

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Table 3. Diseases of bone remodeling.

5.2. Postmenopausal osteoporosis

Postmenopausal osteoporosis is a common disease with a spectrum ranging from asymptomatic bone loss to disabling hip fracture (Table 3). The pathogenesis of postmenopausal osteoporosis is caused primarily by the decline in estrogen levels associated with menopause [93]. Since the establishment of a central role for estrogen deficiency in the pathogenesis of postmenopausal osteoporosis, enormous effort has been focused on elucidating the mecha-
nisms by which estrogens exert their bone-sparing effects. Since the discovery of the RANKL/RANK/OPG axis, it has become clear that estrogen also exerts bone-sparing effects by targeting this regulatory axis. Specifically, estrogen stimulates the expression of OPG in mouse osteoblasts and stromal cells [94]. Moreover, the expression of RANKL was elevated on the surface of bone marrow cells, such as osteoblasts and lymphocytes, from postmenopausal women with osteoporosis compared with cells from premenopausal controls [94]; this finding indicates that RANKL plays an important role in the pathogenesis of postmenopausal osteoporosis.

5.3. Age-related osteoporosis

As the global population ages, the prevalence of age-related osteoporosis (e.g., postmenopausal osteoporosis, male osteoporosis) and related fractures is likely to increase considerably (Table 3). Recent studies indicate that significant trabecular bone loss begins as early as the twenties in men and women long before any major hormonal changes [95]. In women, however, bone loss accelerates for 5 to 10 years after menopause due to the rapid decline in estrogen levels; after this phase, bone loss continues at approximately the same rate as in elderly males. Thus, the pathogenesis of osteoporosis in women involves primarily osteoclasts (bone resorption) and results from changes in estrogen and FSH levels at menopause and age related, is centered on osteoblasts (bone formation), and engages a number of distinct factors associated with the aging process in both men and women. Thus, age-related changes in the activity of either cell type may lead to bone loss [96]. Age-related osteoporosis in men also has a multifactorial etiology. The decreased bone formation caused by changes in ROS, IGF-1, and PTH levels associated with aging plays a predominant role in the pathogenesis of age-related osteoporosis in men. However, age-related changes in the levels of sex steroids, including both estrogen and androgen, also contribute to the pathogenesis of age-related osteoporosis in men [97].

5.4. Glucocorticoid-induced osteoporosis

Glucocorticoids (GCs) are potent immunomodulatory drugs that are commonly used to treat a variety of inflammatory conditions and autoimmune disorders. GCs increase bone resorption and reduce bone formation (Table 3) [98]. Pharmacological doses of GCs induce osteoporosis primarily by altering normal bone remodeling. GCs exert deleterious effects on the differentiation, function, and survival of multiple cell types involved in the remodeling process. GCs have profound effects on osteoblast differentiation and function. As in other target tissues, glucocorticoids exert their effects on gene expression via cytoplasmic glucocorticoid type 2 receptors. In adult bone, functional glucocorticoid receptors are found in pre-osteoblast/stromal cells, osteoblasts (the cells that produce bone matrix), but not in osteoclasts [99]. Instead, glucocorticoids stimulate osteoclast proliferation by suppressing synthesis of osteoprotegerin, an inhibitor of osteoclast differentiation from hematopoietic cells of the macrophage lineage, and by stimulating production of the receptor activator of nuclear factor kappa-B (RANK), which is required for osteoclastogenesis. High glucocorticoid levels also stimulate RANKL synthesis by pre-osteoblast/stromal cells, supporting osteoclast differentiation and net bone resorption [100].
5.5. Immobilization-induced osteoporosis

One of the major functions of bone remodeling is to adapt bone material and structural properties to the mechanical demands that are placed on the skeleton, including mechanical loading and weight bearing (Table 3). The importance of the mechanical balance of bone has been more recently stressed by the research on the effect of weightlessness on bone, and by the introduction of the concept of "mechanostat" in the pathogenesis of osteoporotic conditions. Immobilization osteoporosis has clinical (fractures, sometimes hypercalcemia, urinary lithiasis) and radiological features. Immobilization has an effect on bone modeling and remodeling, through an increased activation of remodeling loci, and a decrease of the osteoblastic stimulus. For ordinary individuals, the skeleton is developed in childhood and then constantly remodeled throughout adulthood to maintain mechanical strength that can sufficiently support normal weight bearing and routine physical activities. However, for individuals such as athletes, the mechanical needs increase for certain regions of the skeleton; consequently, bone modeling results in the formation of stronger bone to replace old bone that could not adequately meet the increased mechanical demands [101].

5.6. Renal osteodystrophy

Renal osteodystrophy the term used to describe a heterogeneous group of metabolic bone diseases that accompany chronic kidney disease, is a multifactorial disorder of bone remodeling (Table 3). The bone disorders in renal osteodystrophy include: osteomalacia of adults and rickets of children (so-called "renal rickets"); osteitis fibrosa and other bone changes of secondary hyperparathyroidism; osteopenia; and osteosclerosis. Renal osteodystrophy is an alteration of bone morphology in patients with CKD (Chronic Kidney Disease). The pathophysiology of renal osteodystrophy is complex and clearly reflects the importance of PTH and vitamin D on bone turnover and related pathological abnormalities. The bone changes are brought about by the abnormal metabolism of vitamin D, the overproduction of parathyroid hormone (PTH), and chronic metabolic acidosis. The diminished renal mass leads to a decreased renal conversion of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D, the active metabolite of vitamin D, resulting in diminished intestinal absorption of calcium, hypocalcemia, and defective bone mineralization characterized by the presence of wide osteoid seams, osteomalacia in adults, and rickets in children [102].

5.7. Paget’s disease

Paget’s disease is known as a bone remodeling disorder and that involves abnormal bone destruction and regrowth, which results in deformity. In Paget’s disease, the bone remodeling process is disregulated (Table 3). New bone is placed where it is not needed, and old bone is removed where it is needed. This disregulation can distort the normal skeletal architecture [103]. Paget’s disease is most commonly diagnosed in the sixth decade, and increases in prevalence as age increases. Paget's disease is very uncommon in individuals under 40 years of age. The most common bones affected by Paget’s disease are the pelvis, femur, spine, skull, and tibia. Paget’s disease is believed to be a primary disorder of increased osteoclast bone resorption with a secondary marked increase in osteoblast activity and new bone formation.
The cause of Paget’s disease is not entirely known, but it is thought to be caused in part from a childhood virus. A virus particle, known as a paramyxovirus nucleocapsid, has been identified within the bone cells of individuals with Paget’s disease. This virus particle is not found in normal bone. Genetics plays a role, several genes have been implicated; however, the most commonly described mutation is a gene that encodes an ubiquitin-binding protein that plays a role in NF-κB signaling [104].

5.8. Osteopetrosis

There are several syndromes of osteopetrosis or osteosclerosis in which bone resorption is defective because of impaired formation of osteoclasts or loss of osteoclast function (Table 3). In these disorders, bone modeling as well as remodeling are impaired, and the architecture of the skeleton can be quite abnormal [105]. Osteopetrosis is a congenital disease that interferes with the formation of the bone marrow, and causes abnormal bone development, blindness, rickets, abnormal tooth development and fragile bones. It results from a defect in cells called osteoclasts, which are necessary for the formation of the bone marrow. In patients with osteopetrosis, osteoclasts not function properly, and no cavity is formed to the bone marrow [106]. The subclassification of these disorders is based upon the mode of inheritance, age of onset, severity, and clinical symptoms [107]. The pathophysiology of osteopetrosis involves mutations that affect osteoclast function. The three most important mutations are: carbonic anhydrase II, proton pump, and chloride channel [48].

6. Conclusions

Bone is a specialized and dynamic tissue, in constant change. It has a complex structure and undergoes constant remodeling. The basic multicellular unit of bone, which comprises osteocytes, osteoclasts and osteoblasts, conducts the remodeling process. In the last years, more knowledge in bone cell biology and genetic studies, have been helped in our understanding of the essential signaling pathways that control bone remodeling and bone mass. They act in a coordinated manner to form or resorb bone. Recent advances in molecular biology and a thorough understanding of the remodeling process bone, many molecules have been discovered that have important roles in bone biology and novel signaling pathways regulating bone remodeling have also been identified. Now understand how PTH, Wnt signaling, and growth factors may trigger anabolic effects in bone. The explosion of this knowledge may serve as a basis for the development of novel therapeutic approaches targeted on the identified signaling molecules enable us to define the abnormalities in cells of the osteoblastic and osteoclastic lineages that lead to bone disease with the hope to the diagnosis and treatment of bone remodeling disorders. With this knowledge, can expect the development of even more therapies to evolve from a better understanding of the complex molecular aspects of bone remodeling.
Author details

Alma Y. Parra-Torres¹,², Margarita Valdés-Flores³, Lorena Orozco⁴ and Rafael Velázquez-Cruz²*

*Address all correspondence to: rvelazquez@inmegen.gob.mx

1 Program in Biomedical Sciences-UNAM, Mexico
2 Genomics of Bone Metabolism Laboratory, National Institute of Genomic Medicine, Mexico City, Mexico
3 Department of Genetics, National Rehabilitation Institute, Mexico City, Mexico
4 Immunogenomics and Metabolic Diseases Laboratory, National Institute of Genomic Medicine, Mexico City, Mexico

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