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Review

Osteoclast–osteoblast communication

Koichi Matsuo *, Naoko Irie

Department of Microbiology and Immunology, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, 160-8582 Tokyo, Japan

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The skeletal system functions and maintains itself based on communication between cells of diverse origins such as osteoclasts and osteoblasts [1,2]. Osteoclasts are derived from hematopoietic stem cells and share precursors with macrophages, whereas cells of the osteoblast lineage such as stromal cells, bone lining cells, osteoprogenitors, preosteoblasts, osteoblasts and osteocytes are derived from mesenchymal stem cells, which also differentiate into fibroblasts, chondrocytes, myoblasts and adipocytes. Osteoclast–osteoblast interactions occur at various stages of differentiation. Around 1997, several laboratories identified the essential osteoclastogenic ligand RANKL (also called TRANCE), a transmembrane glycoprotein belonging to the tumor necrosis factor (TNF)-a[1] superfamily and produced as a trimer by stromal cells. Osteoclast precursors, on the other hand, express RANK, the receptor for RANKL. Prior to identification of RANKL, generation of osteoclasts by co-culturing hematopoietic precursors with stromal cells such as calvarial osteoblasts demonstrated the existence of osteoclast differentiation factor (ODF) [3] or stromal osteoclast-forming activity (SOFA), both of which turned out to be RANKL (reviewed in [4]). Since identification of the gene encoding RANKL, a cocktail of soluble forms of RANKL and macrophage colony-stimulating factor (M-CSF, also known as CSF-1) has been used to generate osteoclast-like cells *in vitro* in the absence of osteoblasts, simplifying analysis of osteoclast differentiation. Besides RANK–RANKL interactions, several molecules mediate communication between osteoclast and osteoblast lineages, and their functions are not limited to triggering osteoclast differentiation. Most notably, osteoclast–osteoblast interaction contributes to coupling of bone resorption and formation. In this review, we discuss osteoclast–osteoblast interactions and describe molecules expressed in distinct phases of bone remodeling.

Osteoclast–osteoblast communication

There are at least three modes of osteoclast–osteoblast communication. Osteoclasts and osteoblasts can make direct contact, allowing membrane-bound ligands and receptors to interact and

* Corresponding author. Fax: +81 3 5360 1508.
E-mail address: matsuo@sc.itc.keio.ac.jp (K. Matsuo).

[1] *Abbreviations used:* BMU, basic multicellular unit; OSCAR, osteoclast-associated receptor; BRC, bone remodeling compartment; TNF, tumor necrosis factor; ODF, osteoclast differentiation factor; SOFA, stromal osteoclast-forming activity; M-CSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; MCP, monocyte chemoattractant protein; IL, interleukin; PTH, parathyroid hormone; SDF, stromal cell-derived factor; NFAT, nuclear factor of activated T cells; NO, nitric oxide; PTHrP, parathyroid hormone-related peptide; PKA, protein kinase A; OPG, osteoprotegerin; LPS, lipopolysaccharide; Ig, immunoglobulin; PIR, paired immunoglobulin-like receptor; ICAM, intercellular adhesion molecule; RGD, arginine-glycine-aspartic acid; TGF, transforming growth factor; BMP, bone morphogenetic protein; IGF, insulin-like growth factor; ARO, autosomal recessive osteopetrosis; TRAP, tartrate-resistant acid phosphatase; TRIP, TGF-b receptor-interacting protein; S1P, sphingosine 1-phosphate; mim, myb induced myeloid protein; PDGF, platelet-derived growth factor; HGF, hepatocyte growth factor; LRP, low-density lipoprotein receptor-related protein; OCIL, osteoclast inhibitory lectin; SLF, steel factor; GPI, glycosyl-phosphatidyl inositol; ROK, Rho-kinase; TCF, T-cell factor; LEF, lymphocyte enhancer factor; EBF, early B-cell factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor.

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initiate intracellular signaling. They can also form gap junctions allowing passage of small water-soluble molecules between the two cell types. Communication can also occur through diffusible paracrine factors, such as growth factors, cytokines, chemokines and other small molecules secreted by either cell type and acting on the other via diffusion. Finally, during bone resorption, osteoclasts may liberate growth factors and other molecules deposited by osteoblasts in bone matrix [5].

Cell culture experiments can distinguish between communication dependent on cell–cell contact and on diffusible factors. For example, osteoblasts fixed with paraformaldehyde can stimulate differentiation of hematopoietic precursors cocultured on these cells, demonstrating direct cell–cell contact [6]. By contrast, a role for a paracrine factor can be demonstrated if that factor crosses a synthetic membrane with a relatively small pore size separating cells in a Transwell plate. These kinds of experiments have demonstrated that hematopoietic precursors differentiate into osteoclasts following direct contact with osteoblasts.

In *in vitro* co-culture systems, osteoclasts differentiate underneath the sheet of osteoblasts and on top of the plastic dishes. In addition, mature multinucleated osteoclasts transmigrate through layers of cells, and transmigration activity is sensitive to inhibitors of c-src and matrix metalloproteinases (MMPs) [7]. Osteoclasts recognize the bone surface, especially collagens and minerals, and form the sealing zone and actin ring, while on a plastic surface osteoclasts do not form proper actin rings [8]. Some researchers use dentine or bovine bone slices with *in vitro*-generated resorption lacunae to analyze the potential regulatory effect of resorption lacunae on osteoblastic bone formation. Collectively, accumulating evidence indicates that all three modes of communication—direct, paracrine, and cell–bone matrix—regulate bone remodeling.

Three phases of bone remodeling

In bone remodeling, bone resorption by osteoclasts is followed by osteoblastic bone formation, so that resorbed lacunae are filled to the original level by osteoblasts. Bone remodeling has been described as a "bone remodeling cycle" consisting of activation, resorption, reversal, and formation phases [9]. However, in terms of osteoclast–osteoblast communication, it may be more convenient to view bone remodeling as occurring in three phases: initiation, transition, and termination of remodeling (Fig. 1). The directions of major communication are opposite between initiation and transition phases: from osteoblasts to osteoclast precursors in initiation, and from osteoclasts to osteoblast precursors (or bidirectionally) in transition. The initiation phase includes recruitment of osteoclast precursors, differentiation and activation of osteoclasts, and maintenance of bone resorption. Osteoclastic bone resorption lasts about three weeks in human bone. The transition phase is a period when osteoclastic bone resorption is inhibited, osteoclasts undergo apoptosis, and osteoblasts are recruited and differentiate. The resorbed surface is prepared for bone formation that follows ("reversal" of bone resorption into formation [10–13]) in the transition phase. The termination phase includes new bone (osteoid) formation, mineralization and entry into quiescence. The termination phase is much longer than the initiation phase since osteoblastic bone formation, which lasts about three months in humans, is a much slower process than osteoclastic bone resorption. During the termination phase, osteoclastic differentiation is apparently inhibited.

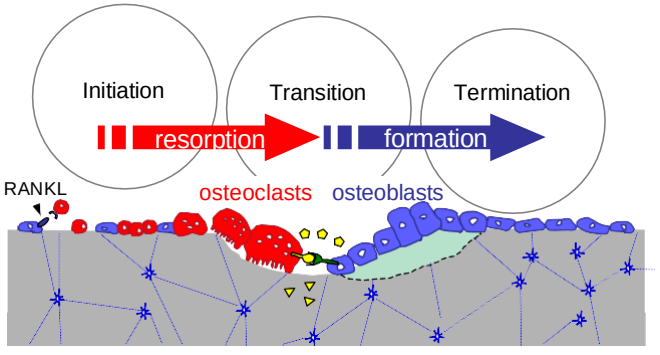


Fig. 1. Three-phase model of bone remodeling. Cells in osteoclast (red) and osteoblast (blue) lineages are shown. Osteocytes (star-shaped) and canaliculi (blue lines) are also shown in bone (gray). Initiation starts with recruitment of hematopoietic precursors. Osteoclast differentiation is induced by osteoblast lineage cells expressing osteoclastogenic ligands such as RANKL. Osteoclasts become multinucleated and resorb bone. Transition is marked by switching from bone resorption to formation via coupling factors, possibly including diffusible factors (yellow pentagons), membrane bound molecules (yellow lollipops), and factors embedded in bone matrix (yellow triangles). The termination phase ensures that the resorbed lacuna is refilled due to the bone-forming activity of osteoblasts, and osteoblasts flatten to form a layer of lining cells over new bone.

Initiation phase

Osteoclast–osteoblast communication occurs in the BMU, a site for bone remodeling generated asynchronously at various places in the skeleton. Initiation of osteoclastogenesis largely depends on interaction between osteoclast precursors and cells in the osteoblast lineage. Bone lining cells, which express RANKL and stimulate RANK on osteoclast precursors, are flat and not bone-forming, while osteoblasts are round or cuboidal, and actively form osteoid. Osteoblasts produce M-CSF, which is required for survival of cells in the macrophage–osteoclast lineage [14,15]. M-CSF also controls cell migration and cytoskeletal reorganization in macrophages and osteoclasts, both of which express c-Fms, the tyrosine kinase receptor for M-CSF [16].

Recruitment by chemokines

How do osteoclast precursors find a specific bone surface to differentiate on? And to what extent do cells in the osteoblast lineage determine positioning of circulating osteoclast precursors onto bone surface? Bone remodeling takes place in response to different stimuli, including generation of bone microcracks, loss of mechanical loading, low blood calcium, alterations in hormones and cytokines. It is possible that recruitment of osteoclast precursors *per se* is rate limiting.

Chemokines are chemotactic cytokines stimulating recruitment of monocytes and other leukocytes, and they are likely to be secreted by stromal cells or bone lining cells to recruit osteoclast precursors. Monocyte chemoattractant protein-1 (MCP-1, also known as CCL2) is produced by osteoblasts and is a candidate recruiter of osteoclast precursors [17,18]. While inflammatory cytokines such as TNF-a and Interleukin (IL)-1b induce MCP-1 expression in osteoblasts, MCP-1 is expressed in osteoblasts even in the absence of inflammation, such as during tooth eruption [17] and in response to parathyroid hormone (PTH) [18]. In osteoclast precursors, expression of MCP-1 receptors is induced by RANKL [19], suggesting that osteoblasts can enhance MCP-1-dependent recruitment through RANKL. Besides MCP-1, stromal cell-derived factor (SDF-1, also known as CXCL12) is thought to recruit osteoclast precursors [18]. SDF-1 is a chemokine produced by bone vascular endothelial and marrow stromal cells, which binds to osteoclast precursors expressing the chemokine receptor CXCR4 and induces MMP-9 expression [20,21]. Interestingly, proteolytic activity of mature CXCR4-positive osteoclasts promotes mobilization of hematopoietic progenitors by degrading SDF-1 and osteopontin in endosteum regions in response to stress [22].

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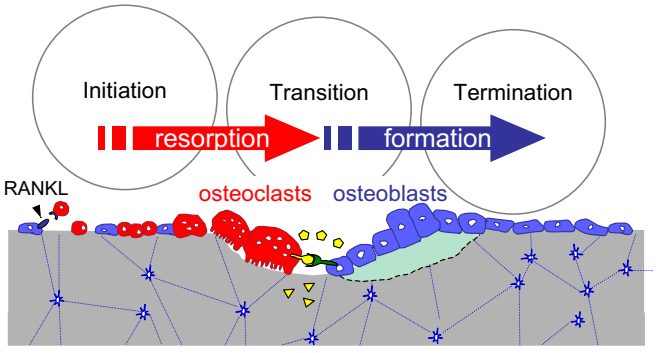


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Nuclear factor of activated T-cells c1 (NFATc1) is a transcription factor essential for osteoclast differentiation [23] and also important in the osteoblast lineage [24]. Mice overexpressing constitutively active NFATc1 in osteoblasts develop high bone mass. Osteoblasts in these mice secrete the monocyte chemoattractants CCL8 (MCP-2), CCL6 (MRP-1) and CCL12 (MCP-5), and the mice exhibit greatly increased numbers of osteoclasts [25]. Therefore, several chemokines appear to be used by osteoblasts to communicate with osteoclast precursors.

Positioning by osteocytes

Osteocytes, cells derived from osteoblasts embedded in bone matrix, are likely to determine which bone surface osteoclasts will resorb. Both microcracks and loss of mechanical loading can be sensed by osteocytes, the third major cellular component of bone remodeling [26,27]. Osteocytes are interconnected in the bone matrix through a network of osteocyte canaliculi approximately 130–390 nm in diameter [28] containing osteocyte dendritic processes. Dendritic processes radiating from osteocytes toward the bone surface are more numerous and much longer than those radiating internally [29]. In other words, osteocytes can polarize along the axis towards the bone surface where they contact osteoblasts or bone lining cells. It has been proposed that microfractures and microcracks in bone are first detected by osteocytes, which then trigger osteoclast differentiation [30]. Apoptotic osteocytes may secrete regulatory factors that reach bone surface to induce osteoclast differentiation, initiating repair. Indeed, there is a high, positive correlation between remodeling indices and apoptotic osteocyte density [31].

Alternatively, osteocyte networks may actively inhibit osteoclastic bone resorption by default, and osteocyte apoptosis due to microcrack damage may induce osteoclastogenesis by switching off such negative signals. In fact, a computational bone adaptation model revealed that if one assumes that strain-induced osteocytic signals both inhibit osteoclast activity and stimulate osteoblast activity, one can simulate key aspects of BMU-based remodeling in both cortical and trabecular bone [32,33]. What might be the anti-osteoclastogenic molecule produced by osteocytes? One candidate is transforming growth factor (TGF)-b, which is produced by the established osteocyte-like cell line MLO-Y4 [34] and suppresses osteoclastogenesis by reducing RANKL-expression by osteoblasts [35]. Osteocytes may produce nitric oxide (NO) in response to physiological mechanical stress, preventing initiation of osteoclastogenesis [36].

RANKL and costimulatory molecules

Interaction between RANK-expressing osteoclast precursors and RANKL-expressing osteoblasts is essential for osteoclastogenesis. RANK signaling activates an osteoclastogenic cascade of transcription factors including NF-jß, AP-1 (c-Fos) and NFATc1. Mice lacking RANKL lack osteoclasts [37,38], and injection of a soluble form of RANKL rapidly induces osteoclast formation and bone resorption, even in wild-type mice [39]. Several soluble factors can enhance osteoclastogenesis through RANKL induction in osteoblasts. Such factors include PTH, parathyroid hormone-related peptide (PTHrP), TNF-a, IL-1, IL-11, thyroid hormone, 1,25-$(OH)_2$ vitamin D_3 and prostaglandin E_2. Most modulate the cyclic AMP/protein kinase A (PKA) pathway.

Osteoblasts also express a decoy RANKL receptor, osteoprotegerin (OPG), which inhibits RANK signaling by masking RANKL [40,41]. Thus, OPG interferes with osteoclast–osteoblast interactions, and the RANKL/OPG ratio is indicative of osteoclastogenic activity in various bone remodeling diseases. Lipopolysaccharide (LPS) rapidly increases serum OPG levels in mice, but the mechanism and biological significance of rapid OPG induction seen during bacterial infection is unclear [42]. Below, we discuss potential regulatory roles of OPG during the termination phase of bone remodeling.

Osteoclast precursors express immunoglobulin (Ig)-like receptors, or immunoreceptors, which synergize with RANK signaling as costimulatory molecules. [43]. Immunoreceptors such as OSCAR [44] and paired immunoglobulin-like receptor (PIR)-A are associated with the adaptor protein FcRc, which delivers downstream osteoclastogenic signals. Unknown ligands on osteoblasts stimulate OSCAR through cell–cell interaction [45]. Ligands for another subset of immunoreceptors associated with adaptor DAP12 instead of FcRc are expressed on osteoclast precursors themselves and, therefore, stimulation is not dependent on osteoblasts. Mice lacking both DAP12 and FcRc are osteopetrotic due to absence of immunoreceptor signaling [43,46].

Semaphorins and their receptors function in axon guidance like ephrins and netrins, as well as in imuune cell interactions [47]. The primary receptors for semaphorins are members of the plexin family. Mice lacking plexin-A1, a receptor for the transmembrane semaphorin 6D (Sema6D), show defects in both dendritic cells and osteoclasts, presumably through impaired immuno-receptor signaling [48]. Other semaphorins such as semaphorin 7A (Sema7A), semaphorin 3A (Sema3A), and semaphorin D4 (Sema4D) are also expressed in bone cells and may mediate osteoclast–osteoblast communication [49–51].

Osteoclast–bone matrix interaction

Bone lining cells, which express intercellular adhesion molecule-1 (ICAM-1) unlike osteoblasts, may predispose or clean bone surface through MMP activity prior to osteoclastic bone resorption [52,53]. Osteoclasts use integrin avb3 to interact with vitronectin, fibronectin and osteopontin in bone matrix [54]. Generally, integrin receptors are heterodimers composed of a and b chains, which recognize arginine-glycine-aspartic acid (RGD) sequences in extracellular matrix proteins. Mice lacking the b3 integrin subunit develop osteopetrosis with aging. These mice exhibit greater numbers of osteoclasts but with a reduced ability to resorb than do heterozygotes, indicating that avb3 is not required for osteoclastogenesis but is essential for osteoclast function [55].

Osteoclasts and their precursors express integrin a9b1, which is required for actin ring reorganization and bone resorption [56]. Interaction of a9b1 with a metallo-protease, ADAM8, which lacks an RGD sequence and is expressed in both osteoblasts and osteoclasts [57], stimulates osteoclast formation [58].

Transition phase

During transition phase, a period critical for "coupling", bone-resorbing osteoclasts stimulate differentiation of osteoblast precursors, activating bone formation in bone resorption lacunae. While bone formation is being activated, osteoclastic bone resorption stops and osteoclasts undergo apoptosis in a Bim/caspase-3-dependent manner [59] or through estrogen-induced Fas ligand [60]. High extracellular calcium released from bone during resorption induces osteoclast apoptosis [61–63].

Coupling

A special mechanism determines the transition from bone resorption to formation at the cellular level [64,65]. Coupling occurring microscopically in the BMU is the basis for coupling in the entire body. When calcium loss from bone is quantified and plotted against calcium accretion, bone resorption and formation

Nuclear factor of activated T-cells c1 (NFATc1) is a transcription factor essential for osteoclast differentiation [23] and also important in the osteoblast lineage [24]. Mice overexpressing constitutively active NFATc1 in osteoblasts develop high bone mass. Osteoblasts in these mice secrete the monocyte chemoattractants CCL8 (MCP-2), CCL6 (MRP-1) and CCL12 (MCP-5), and the mice exhibit greatly increased numbers of osteoclasts [25]. Therefore, several chemokines appear to be used by osteoblasts to communicate with osteoclast precursors.

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Osteoclast precursors express immunoglobulin (Ig)-like receptors, or immunoreceptors, which synergize with RANK signaling as costimulatory molecules. [43]. Immunoreceptors such as OSCAR [44] and paired immunoglobulin-like receptor (PIR)-A are associated with the adaptor protein FcRγ, which delivers downstream osteoclastogenic signals. Unknown ligands on osteoblasts stimulate OSCAR through cell–cell interaction [45]. Ligands for another subset of immunoreceptors associated with adaptor DAP12 instead of FcRγ are expressed on osteoclast precursors themselves and, therefore, stimulation is not dependent on osteoblasts. Mice lacking both DAP12 and FcRγ are osteopetrotic due to absence of immunoreceptor signaling [43,46].

Semaphorins and their receptors function in axon guidance like ephrins and netrins, as well as in imuune cell interactions [47]. The primary receptors for semaphorins are members of the plexin family. Mice lacking plexin-A1, a receptor for the transmembrane semaphorin 6D (Sema6D), show defects in both dendritic cells and osteoclasts, presumably through impaired immuno-receptor signaling [48]. Other semaphorins such as semaphorin 7A (Sema7A), semaphorin 3A (Sema3A), and semaphorin D4 (Sema4D) are also expressed in bone cells and may mediate osteoclast–osteoblast communication [49–51].

Osteoclast–bone matrix interaction

Bone lining cells, which express intercellular adhesion molecule-1 (ICAM-1) unlike osteoblasts, may predispose or clean bone surface through MMP activity prior to osteoclastic bone resorption [52,53]. Osteoclasts use integrin αvβ3 to interact with vitronectin, fibronectin and osteopontin in bone matrix [54]. Generally, integrin receptors are heterodimers composed of α and β chains, which recognize arginine-glycine-aspartic acid (RGD) sequences in extracellular matrix proteins. Mice lacking the β3 integrin subunit develop osteopetrosis with aging. These mice exhibit greater numbers of osteoclasts but with a reduced ability to resorb than do heterozygotes, indicating that αvβ3 is not required for osteoclastogenesis but is essential for osteoclast function [55].

Osteoclasts and their precursors express integrin α9β1, which is required for actin ring reorganization and bone resorption [56]. Interaction of α9β1 with a metallo-protease, ADAM8, which lacks an RGD sequence and is expressed in both osteoblasts and osteoclasts [57], stimulates osteoclast formation [58].

Transition phase

During transition phase, a period critical for "coupling", bone-resorbing osteoclasts stimulate differentiation of osteoblast precursors, activating bone formation in bone resorption lacunae. While bone formation is being activated, osteoclastic bone resorption stops and osteoclasts undergo apoptosis in a Bim/caspase-3-dependent manner [59] or through estrogen-induced Fas ligand [60]. High extracellular calcium released from bone during resorption induces osteoclast apoptosis [61–63].

Coupling

A special mechanism determines the transition from bone resorption to formation at the cellular level [64,65]. Coupling occurring microscopically in the BMU is the basis for coupling in the entire body. When calcium loss from bone is quantified and plotted against calcium accretion, bone resorption and formation

are largely balanced, even in patients with calcium metabolism disorders [66]. How bone resorption stimulates an equivalent bone formation has interested bone biologists, who have proposed coupling mechanisms to account for this phenomenon. These activities occur when liberated, secreted or membrane-bound molecules produced by osteoclasts act on osteoblast precursors to stimulate bone formation in remodeling [1] (Table 1). Specialized vascular structures on the surface of trabecular and cortical bone known as BRCs are likely sites of bone remodeling [67] (see below).

Liberated coupling factors

Activation of osteoblastic bone formation by osteoclasts, a critical step in coupling, could occur without cell–cell contact. Osteoclastic bone resorption may liberate growth factors such as TGF-b, bone morphogenetic proteins (BMPs) and insulin-like growth factor (IGF)-II from bone matrix [5,68], which in turn activate osteoblastic bone formation. However, several lines of evidence suggest that osteoclast bone resorptive activity is dispensable for coupling [69]. During bone resorption osteoclasts secrete both hydrochloric acid, to resorb hydroxyapatite, and proteases like cathepsin K to degrade collagen and other bone matrix proteins. Acidification of resorption lacunae is impaired in patients with infantile malignant autosomal recessive osteopetrosis (ARO) who carry inactivating mutations in the a3 subunit of the proton pump *TCIRG1* (or *ATP6i*) [70,71] or in the chloride channel 7 [72]. Similarly, acidification is similarly impaired in Atp6i-deficient mice [73]. However, ARO patients and the mouse models exhibit increased numbers of osteoclasts, which can stimulate bone formation [74,75]. This suggests that osteoclast number, not bone resorption, is critical to stimulate bone formation.

A rare recessive osteosclerotic disease, odysostosis, is caused by inactivating mutations in the human cathepsin K gene (*CTSK*) [76,77]. A similar condition is seen in mice lacking the cathepsin K gene [78,79]. Whether and how bone formation is affected in odysostosis is currently unclear. Recently, it is postulated that cathepsin K may degrade bone matrix-derived growth factors, and, in the presence of cathepsin K inhibitors, these growth factors may be released intact to augment bone formation [80].

Secreted coupling factors

Coupling mechanisms induce bone formation in resorption lacunae. Local topography alone, such as grooves and resorption pits, induces bone formation by enhancing cellular condensation [81]. Alternatively, osteoblasts may recognize components of previously resorbed lacunae in the absence of osteoclasts. Type V tartrate-resistant acid phosphatase (TRAP, encoded by *Acp5*) is required for bone matrix resorption and collagen turnover [82,83]. Curiously, transgenic mice overexpressing TRAP show not only decreased trabecular bone volume but also increased bone formation [84], suggesting that TRAP, which usually coats resorption lacunae, may stimulate bone formation. Sheu et al. used phage display to screen an osteoblast expression library for sequences binding to TRAP in search for osteoblastic proteins accounting for why osteoblastic bone formation occurs in resorption lacunae. TGF-b receptor-interacting protein (TRIP-1) is a candidate protein identified [85,86].

Production of putative coupling factor(s) may be increased in vacuolar H^+-ATPase V0 domain subunit d2 (*Atp6v0d2*)-deficient mice, which show markedly increased bone mass and enhanced bone formation [87]. Atp6v0d2 is expressed in osteoclasts and required for osteoclast fusion. Since Atp6v0d2 is not expressed in osteoblasts and does not affect osteoblast differentiation *in vitro*, increased bone formation in mice lacking Atp6v0d2 is probably due to coupling factors produced by osteoclasts.

Several *in vitro* studies propose potential coupling factors secreted by osteoclasts, including sphingosine 1-phosphate (S1P), myb-induced myeloid protein-1 (mim-1), a B polypeptide chain platelet-derived growth factor homodimer (PDGF BB), and hepatocyte growth factor (HGF) (see below). S1P is produced by sphingosine kinase (*Sphk*) in osteoclasts and can act as both an intracellular and extracellular messenger. Secreted S1P interacts with the S1P receptor expressed on osteoblasts and enhances RANKL expression as well as migration and survival of osteoblasts [88]. Osteoclasts secrete abundant mim-1, a 35-kD protein, and secretion is enhanced by phorbol myristate acetate treatment [89]. PDGF BB promotes proliferation but suppresses differentiation of osteoblast precursors [90,91]. When osteoclasts undergo apoptosis, reduced PDGF BB secretion may contribute to a switch from proliferation to differentiation seen in osteoblasts. HGF, secreted by osteoclasts

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IGF-II (matrix)[a]	?	IGF R	Unknown	Enhances bone formation	[5,68]
Cathepsin K	?	Unknown	Unknown	Enhances/inhibits bone formation	[78,79,132]
TRAP	?	GPC4 homolog, TRIP-1	Unknown	Enhances differentiation	[84–86]
Atp6v0d2	?	Unknown	Fusion	Suppresses bone formation	[87]
Sphingosine 1-phosphate (S1P)	?	S1P receptor	Attenuates differentiation (intracellular S1P)	Stimulates migration and survival, induction of RANKL (secreted S1P)	[88]
mim-1	?	Unknown	Unknown	Induces proliferation	[89]
PDGF BB	?	PDGF Receptor	Inhibits Differentiation by OPG	Suppresses Differentiation	[90,91]
HGF	?	HGF receptor	Stimulates migration and DNA replication	Stimulates DNA synthesis and proliferation	[92]
Wnt?	?	Frizzled, LRP5	Unknown	Enhances differentiation	[93,94]
OCIL	?	?	Unknown	Inhibits differentiation	[99]
?		OCIL	Inhibits differentiation	Unknown	[96,97]
c-Kit		SLF (membrane bound)	Suppresses differentiation	Enhances bone formation	[101]
ephrinB2	M	EphB4	Inhibits differentiation	Enhances differentiation	[103]
Connexin	M	Connexin	Regulates differentiation	Enhances differentiation and bone formation	[112]

?, signals from osteoclasts to osteoblasts. , from osteoblasts to osteoclasts. M, bidirectional.

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but not osteoblasts, binds to HGF receptors expressed on both osteoblasts and osteoclasts [92]. HGF treatment increases DNA synthesis and proliferation of both cell types.

If osteoclasts produce coupling factors enhancing osteoblast differentiation, these factors might stimulate Wnt signaling in osteoblasts. An inactivating mutation in the gene encoding cell surface low-density lipoprotein receptor-related protein (LRP) 5, a Wnt co-receptor, results in decreased bone formation manifested as osteoporosis-pseudoglioma syndrome in humans and mouse, suggesting that Wnt signaling promotes bone formation. Conversely, activating mutations in LRP5—notably a glycine-to-valine change at amino acid 171—result in high bone mass phenotypes in humans and mouse (reviewed in [93]). Wnt10b increases postnatal bone formation by enhancing osteoblast differentiation in transgenic mice in bone marrow and adipose tissue [94] or in osteoblasts [95]. A possible link between coupling factors and Wnt signaling should be examined in future studies.

Membrane bound molecules

Osteoclast inhibitory lectin (OCIL) is a type II transmembrane C-type lectin that suppresses osteoclast differentiation [96,97]. Curiously, osteoclast inhibitory activity of OCIL is independent of sugar recognition, even though OCIL binds several physiologically important glycosaminoglycans [98]. OCIL inhibits osteoblast differentiation and function *in vitro* [99]. Since many membrane proteins expressed on osteoclasts or osteoblasts are glycoproteins, critical roles for glycosylation in osteoclast–osteoblast communication must be investigated.

Steel factor (SLF) (also known as stem cell factor, SCF, mast cell growth factor, or MGF, and encoded by *Kitl*) is the ligand for the tyrosine kinase receptor c-Kit (also known as CD117). The mouse Steel-Dickie (*Sl*^{d}) mutation is a 4.0-kb intragenic deletion removing the transmembrane and cytoplasmic domains and encoding a biologically active, soluble form of SLF [100]. Young mice with this mutation show delayed bone growth, osteopenia, impaired osteoblast function and increased osteoclast surface, suggesting that membrane-bound but not soluble SLF suppresses osteoclast formation and enhances bone formation by osteoblasts [101].

Bidirectional signaling between osteoclasts and osteoblasts

Eph tyrosine kinase receptors and ligands function in various developmental processes including neuronal axon guidance and angiogenesis [102]. Eph receptors are classified in two sub-groups, EphBs (EphB1–B6) and EphAs (EphA1–A8), while their membrane-bound ligands, the ephrins, are subdivided into the ephrinBs (ephrinB1–B3) and ephrinAs (ephrinA1–A6). EphrinB family molecules are transmembrane proteins, while ephrinA proteins are glycosylphosphatidyl inositol (GPI)-anchored. Ligands ephrinB and ephrinA bind to tyrosine kinase receptors EphB and EphA, respectively. Interaction between ephrin- and Eph-expressing cells results in bidirectional signal transduction. Reverse signaling through the ephrinB2 ligand into osteoclasts suppresses differentiation, while forward signaling through the EphB4 receptor into mesenchymal precursors promotes osteoblast differentiation (Fig. 2) [103]. Reverse signaling through ephrinB2 suppresses osteoclastogenesis by blocking expression of the transcription factor c-Fos, while c-Fos overexpression rescues osteoclast differentiation in the presence of the inhibitory reverse signaling. How transcription of c-Fos is blocked by reverse signaling is currently unclear. However, enhanced osteoblast differentiation mediated by EphB4 forward signaling likely results from inhibition of RhoA activity in mouse cells [103]. This finding is consistent with the observation that inhibitors of Rho-kinase (ROK) signaling stimulate osteoblast differentiation in primary mouse calvarial osteoblasts [104]. Interestingly, in human cells RhoA has the opposite function: inhibiting RhoA suppresses osteoblast differentiation [105]. The molecular basis for this species difference remains to be determined. Since ephrinB2 is expressed in mature osteoclasts and EphB4 is expressed by osteoblast precursors, we hypothesized that ephrinB2/EphB4 interaction facilitates the transition from bone resorption to formation [103,106].

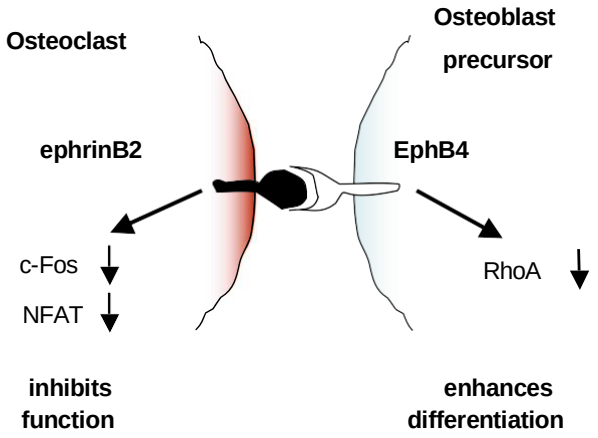


Fig. 2. Bidirectional signaling mediated by ephrinB2 on osteoclasts and EphB4 on osteoblast precursors. Reverse signaling through ephrinB2 into the osteoclast suppresses osteoclast function by reducing c-Fos and NFATc1 activities, while forward signaling through EphB4 into the osteoblast precursor enhances osteoblast differentiation by reducing RhoA activity [103].

Direct osteoclast–osteoblast contact in vivo

Everts and colleagues reported that proteolytic removal of bone collagen left by osteoclasts in resorption lacunae (Howship's lacunae) is an obligatory step linking bone resorption and bone formation [107]. They found that almost all osteoclasts attached to bone surface were in close contact with bone lining cells [107]. In bone samples of odysostosis patients or mice lacking cathepsin K [78,108], bone lining cells were frequently found at sites where osteoclasts were retracting [107]. Although not widely accepted, it is possible that mature bone resorbing osteoclasts may interact not only with bone lining cells but also with fully differentiated osteoblasts. Our own preliminary observations using transmission electron microscopy detected cell–cell contact between mature osteoclasts, which exhibit a ruffled border, and mature osteoblasts, containing abundant endoplasmic reticulum, in the metaphyseal region of mouse tibia (Fig. 3). Detailed quantitative analysis of cell–cell contact between mature osteoclasts and cells in the osteoblast lineage at various differentiation stages will be required to evaluate the importance of cell–cell interaction during the transition phase.

The transition phase corresponds to and includes the so-called "reversal" phase in bone remodeling. Is the idea of cell–cell contact between osteoclasts and osteoblasts at the transition phase consistent with the concept of a reversal phase in bone remodeling? The reversal phase has been extensively analyzed using rat alveolar bone, in which high turnover remodeling can be experimentally induced [10,11]. In this model, only macrophagic mononuclear cells were observed in resorption lacunae between resorption and formation. These cells degrade demineralized matrix left on resorbed surfaces and form reversal lines [12,13]. However, histological and cell culture experiments suggest that osteoblast-like cells remove remaining organic matrix in lacunae before depositing new collagen fibrils at the bottom of lacunae [107,109], suggesting that cells in resorption lacunae may be osteoblast precursors or lining cells.

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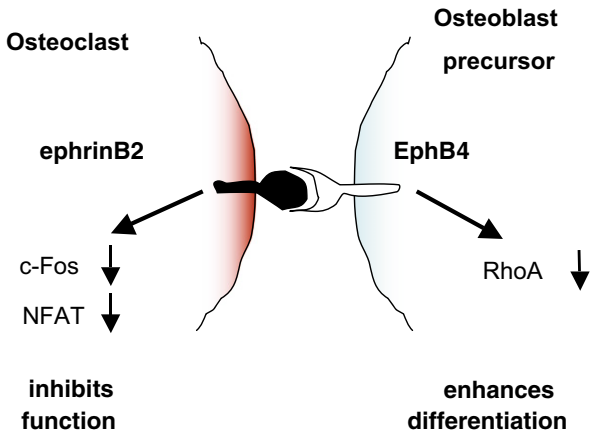


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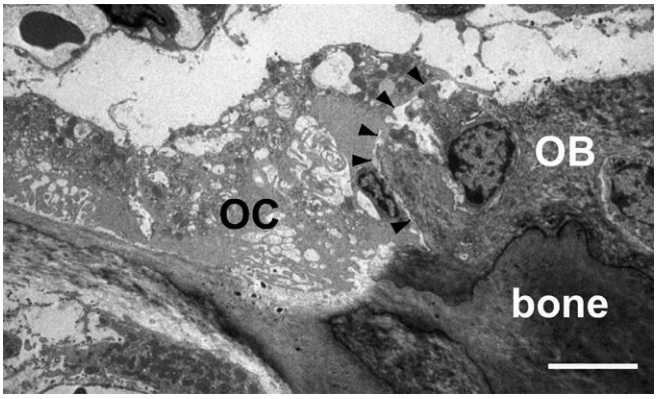


Fig. 3. Transition electron micrograph of osteoclast–osteoblast contact in mouse tibial bone marrow (14-week-old male). Arrowheads indicate a contact surface between osteoclasts (OC) and osteoblasts (OB). Scale bar, 5 1m.

A sinus or compartment in bone marrow, termed BRC, is a possible locus for bone remodeling comprising the BMU [67,110,111] (Fig. 4). According to this concept, osteoclasts on cancellous bone surface are covered by an outer sheet of flat lining or stromal cells positive for osteoblast markers such as alkaline phophatase, osteocalcin, type I collagen, RANKL or OPG [67]. Thus, the BRC consists of a canopy of lining cells and the BMU underneath on the bone surface. The BRC can be considered a structure ensuring osteoclast-osteoblast interaction throughout bone remodeling. Cell-cell contact between osteoclasts and lining cells of the osteoblast lineage on top of osteoclasts in the BRC may occur (Fig. 4c), in addition to side-by-side contacts on the bone surface (Fig. 1).

Gap junction communication between osteoblasts mediated by connexin stimulates osteoblast differentiation and bone formation. Connexin expression in osteoclasts has also been identified. Gap junction intercellular communication is also important for osteoclast formation and survival. These results lead to the hypothesis that Gap junction-mediated intercellular communication between osteoclasts and osteoblasts may occur when cells are adjacent to one another [112].

Termination phase

Once osteoblastic bone formation begins, bone formation proceeds slowly and lasts much longer (about three months) than resorption (about three weeks). Osteocytes produce sclerostin (encoded by *Sost*), which suppresses osteoblastic bone formation [113]. Loss-of-function mutations in human sclerostin result in excess bone formation, a condition known as sclerosteosis [114,115]. Osteoblasts become quiescent presumably with the help of sclerostin secreted through osteocyte canaliculi. During bone formation in the termination phase, osteoclast differentiation is suppressed, most likely through OPG produced by osteoblasts.

OPG production

As discussed above, canonical Wnt signaling stimulates osteoblast differentiation in osteoprogenitors and bone formation in differentiated osteoblasts [116]. Wnt signaling inhibits degradation of b-catenin in cytoplasm, and b-catenin interacts with T-cell factor (TCF)/lymphocyte enhancer factor (LEF) proteins to regulate transcription of the OPG gene, among others. b-catenin overexpression in differentiated mouse osteoblasts results in osteopetrosis, while osteoblast-specific deletion of b-catenin causes low bone mass due to increased osteoclast activity [117,118]. These data indicate that canonical Wnt signaling through b-catenin activates the OPG gene promoter in mature osteoblasts, inhibiting osteoclastogenesis [93,118].

Osteoblasts express another transcription factor, early B-cell factor 2 (EBF2), which binds to and activates the OPG promoter synergistically with b-catenin-TCF/LEF [119]. Mice lacking EBF2 show markedly reduced expression of OPG and osteoporosis.

Notch ligands (Delta1, Jagged1 and Jagged2) are expressed in osteoclasts, while osteoblast-specific deletion of Notch1 results in increased numbers of osteoclasts through reduced OPG production [120]. Therefore, osteoclast–osteoblast interaction may induce Notch signaling in osteoblasts, leading to increased OPG production and reduced osteoclastogenesis. Some investigators report that Notch signaling dampens osteoblast formation [121], while others describe opposing phenotypes [122]. On the other hand, Notch1 and Notch3 receptors are expressed throughout osteoclastogenesis. Macrophage/osteoclast-specific deletion of Notch 1, 2 and 3 ($LysMcre^{+}Notch1^{flox/flox}$ $Notch2^{flox/flox}$ $Notch3^{-/-}$) results in increased osteoclast formation and resorptive activity both *in vitro* and *in vivo*, suggesting that Notch signaling inhibits osteoclastogenesis [120,123]. Thus, Wnt signaling, EBF2 activity, and Notch signaling cooperatively attenuate osteoclastogenesis by inhibiting RANK signaling through secretion of OPG by mature osteoblasts.

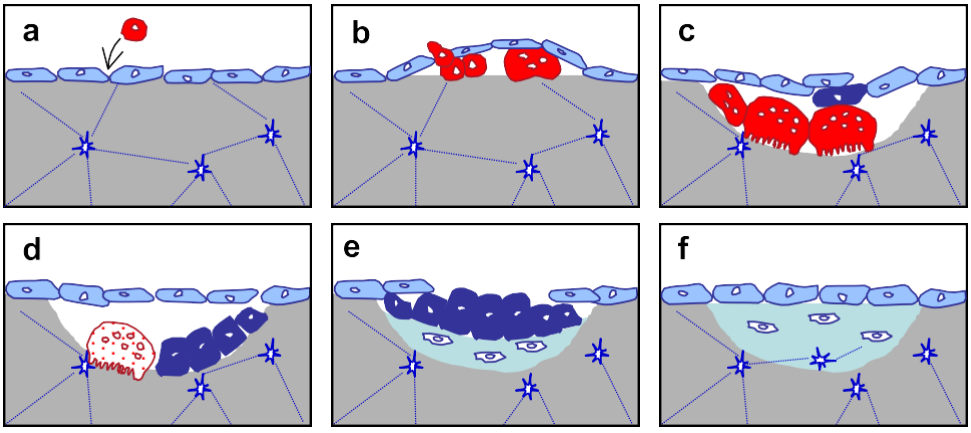


Fig. 4. BMC and possible osteoclast–osteoblast interactions. Cells in osteoclast (red) and osteoblast (light and dark blue) lineages are shown. (a) Recruitment of osteoclast precursors in the early initiation phase. (b) Differentiation of osteoclasts on the bone surface beneath lining cells (light blue) in the initiation phase. (c) Bone resorption by multinucleated osteoclasts, which induce osteoblast differentiation (dark blue) in the transition phase. (d) Osteoclast apoptosis in resorption lacunae in the transition phase. (e) Bone formation by osteoblasts and osteocyte generation in osteoid in the termination phase. (f) Entry into quiescence in the termination phase.

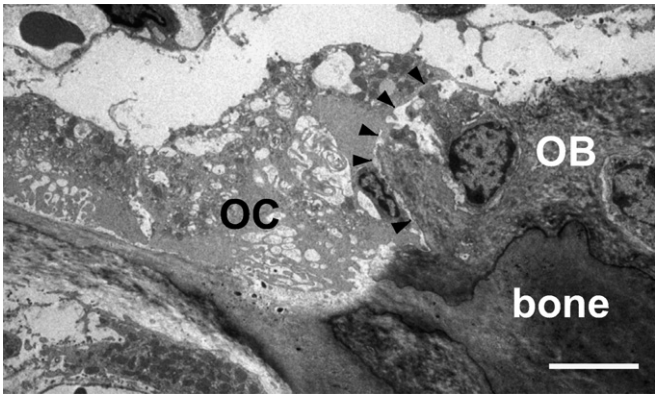


Fig. 3. Transition electron micrograph of osteoclast–osteoblast contact in mouse tibial bone marrow (14-week-old male). Arrowheads indicate a contact surface between osteoclasts (OC) and osteoblasts (OB). Scale bar, 5 μm.

A sinus or compartment in bone marrow, termed BRC, is a possible locus for bone remodeling comprising the BMU [67,110,111] (Fig. 4). According to this concept, osteoclasts on cancellous bone surface are covered by an outer sheet of flat lining or stromal cells positive for osteoblast markers such as alkaline phophatase, osteocalcin, type I collagen, RANKL or OPG [67]. Thus, the BRC consists of a canopy of lining cells and the BMU underneath on the bone surface. The BRC can be considered a structure ensuring osteoclast-osteoblast interaction throughout bone remodeling. Cell-cell contact between osteoclasts and lining cells of the osteoblast lineage on top of osteoclasts in the BRC may occur (Fig. 4c), in addition to side-by-side contacts on the bone surface (Fig. 1).

Gap junction communication between osteoblasts mediated by connexin stimulates osteoblast differentiation and bone formation. Connexin expression in osteoclasts has also been identified. Gap junction intercellular communication is also important for osteoclast formation and survival. These results lead to the hypothesis that Gap junction-mediated intercellular communication between osteoclasts and osteoblasts may occur when cells are adjacent to one another [112].

Termination phase

Once osteoblastic bone formation begins, bone formation proceeds slowly and lasts much longer (about three months) than resorption (about three weeks). Osteocytes produce sclerostin (encoded by *Sost*), which suppresses osteoblastic bone formation [113]. Loss-of-function mutations in human sclerostin result in excess bone formation, a condition known as sclerosteosis [114,115]. Osteoblasts become quiescent presumably with the help of sclerostin secreted through osteocyte canaliculi. During bone formation in the termination phase, osteoclast differentiation is suppressed, most likely through OPG produced by osteoblasts.

OPG production

As discussed above, canonical Wnt signaling stimulates osteoblast differentiation in osteoprogenitors and bone formation in differentiated osteoblasts [116]. Wnt signaling inhibits degradation of β-catenin in cytoplasm, and β-catenin interacts with T-cell factor (TCF)/lymphocyte enhancer factor (LEF) proteins to regulate transcription of the OPG gene, among others. β-catenin overexpression in differentiated mouse osteoblasts results in osteopetrosis, while osteoblast-specific deletion of β-catenin causes low bone mass due to increased osteoclast activity [117,118]. These data indicate that canonical Wnt signaling through β-catenin activates the OPG gene promoter in mature osteoblasts, inhibiting osteoclastogenesis [93,118].

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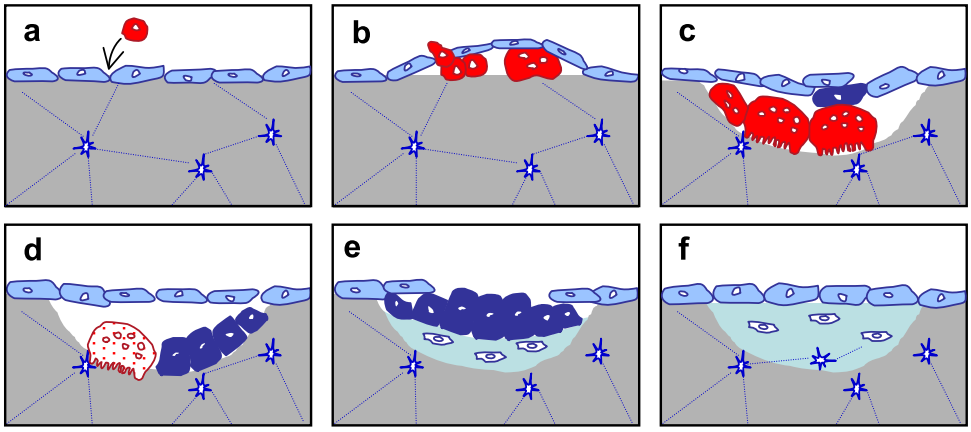


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Besides spatial relationships of bone cells, temporal considerations are important for bone remodeling. OPG function is largely associated with an initiation phase in which OPG counteracts RANKL osteoclastogenic activity. In this review, however, we have explored evidence for a possible role of OPG in the termination phase. OPG may indeed protect osteoid from osteoclastic resorptive activity during bone formation. In addition, specialized bones, such as otic capsule (bone tissue of the inner ear) and the three auditory ossicles in the middle ear are much less remodeled in adult life, presumably due to constitutively high levels of OPG [125,126]. OPG can be viewed as a factor functioning outside of the initiation phase.

Communication between osteoclasts and osteoblasts affects not only bone mass but quality. Excess remodeling associated with aging reduces bone mass, while suppressed bone remodeling increases it. Administration of antiresorptive agents such as bisphosphonates increases bone mass in patients with osteoporosis or other remodeling diseases. However, bone strength is determined not only by mass but by bone quality [127]. Suppressed bone remodeling likely reduces bone quality due to accumulation of microfractures and reduced restructuring of bone architecture [128]. Therefore, understanding osteoclast-osteoblast communication and bone quality is essential to design interventions to prevent bone loss while maintaining bone quality.

Finally, bone cells must communicate with other cells, and dynamic intercellular communication between osteoclasts or osteoblasts and neurons, endothelial cells or other cell types may be critical for bone integrity. Expression of axon guidance molecules such as ephrins, Ephs, semaphorins, netrins and neurotrophins in osteoclasts and osteoblasts [103,129] is consistent with the idea that axon extension by peripheral sensory and sympathetic neurons to osteoblastic or osteoclastic cells may occur [130,131]. Neuronal regulation of bone remodeling has been demonstrated and needs further analysis in terms of bone cell-neuron communication, as does regulation of bone remodeling by the vasculature or by endothelial cells. Endothelial cells also affect bone remodeling by secreting vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), endothelin, and NO. In addition, local acidosis or high H^+ concentrations and hypoxia facilitate initiation of osteoclast differentiation. Future research on intercellular communication during bone remodeling will provide a basis for treating diseases such as osteoporosis, cancer metastasis, and fracture repair.

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