major hormones such as thyroid hormones or cortisol, it has multiple target organs and functions (bone mass, body weight, and reproduction) without a necessary hierarchy among them. However, leptin is unlikely to be the sole central regulator of bone formation. Other yet-to-be discovered centrally acting hormones may positively or negatively regulate bone formation and possibly other aspects of bone physiology.

## Prospects

In the immediate future, studies of osteoblast biology will continue to focus independently on cell differentiation and cell function. In terms of cell differentiation, molecular biology studies and the analysis of other mouse mutant strains should allow us to achieve a more precise understanding of the genetic pathways controlling osteoblast differentiation. These studies will focus on genes located upstream and downstream of *Cbfa1*, but may also reveal other pathways to achieve osteoblast differentiation. In terms of cell function, it is likely that other hormones will be shown to have a role in controlling bone formation, possibly through a central pathway. Likewise, Cbfa1 will probably not remain the only molecule to bridge the "ontogenic gap" between cell differentiation and cell function.

In the long term, it is likely that molecules affecting the function of the osteoblasts will become increasingly important in the quest for new therapies for osteoporosis. Experiments are in progress to test whether increasing Cbfa1 levels will increase bone formation and therefore be potentially useful in preventing or treating osteoporosis. Similarly, inhibitors of the leptin pathway that affect bone mass but not body weight could be beneficial for osteoporosis. The identification of other transcription factors, hormones, or secreted molecules controlling bone formation will increase the likelihood that a successful therapy will be developed for this and other degenerative bone diseases.

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REVIEW

# Bone Resorption by Osteoclasts

**Steven L. Teitelbaum**

**Osteoporosis, a disease endemic in Western society, typically reflects an imbalance in skeletal turnover so that bone resorption exceeds bone formation. Bone resorption is the unique function of the osteoclast, and anti-osteoporosis therapy to date has targeted this cell. The osteoclast is a specialized macrophage polykaryon whose differentiation is principally regulated by macrophage colony-stimulating factor, RANK ligand, and osteoprotegerin. Reflecting integrin-mediated signals, the osteoclast develops a specialized cytoskeleton that permits it to establish an isolated microenvironment between itself and bone, wherein matrix degradation occurs by a process involving proton transport. Osteopetrotic mutants have provided a wealth of information about the genes that regulate the differentiation of osteoclasts and their capacity to resorb bone.**

Osteoclasts are multinucleated cells formed by the fusion of mononuclear progenitors of the monocyte/macrophage family. They are the principal, if not exclusive, resorptive cell of bone, playing a central role in the formation of the skeleton and regulation of its mass. Bone-forming cells, or osteoblasts, have an equally important role in the regulation of bone mass. This cell type is reviewed in a companion article by Ducy *et al.* (*1*). The activity of osteoclasts, relative to bone-forming osteoblasts, dictates the development of osteoporosis, a group of disorders in which skeletal mass has decreased to the point of structural instability, thereby rendering the patient susceptible to spontaneous bone fracture. Because adult osteoporosis, regardless of etiology, always represents enhanced bone resorption relative to formation, progress in understanding the pathogenesis and successful treatment of this family of diseases requires an understanding of osteoclast biology.

Department of Pathology, Washington University School of Medicine, Barnes-Jewish Hospital North, Mailstop 90-31-649, 216 South Kingshighway, St. Louis, MO 63110, USA. E-mail: teitelbs@medicine.wustl.edu

## How Does a Macrophage Become an Osteoclast?

As first noted in 1990, in vitro maturation of macrophages into osteoclasts requires the presence of marrow stromal cells or their osteoblast progeny (*2*). After a decade of confusion, it is now clear that these accessory cells express the two molecules that are essential and sufficient to promote osteoclastogenesis: macrophage colony-stimulating factor (M-CSF) and receptor for activation of nuclear factor kappa B (NF-κB) (RANK) ligand (RANKL)

(also known as OPGL and TRANCE) (Fig. 1). M-CSF (*2*), which is imperative for macrophage maturation, binds to its receptor, c-Fms, on early osteoclast precursors, thereby providing signals required for their survival and proliferation.

Although M-CSF is a secreted product, osteoclastogenesis requires contact between osteoclast precursors and stromal cells or osteoblasts (*2*). Thus, stromal cells and osteoblasts synthesize a surface-residing molecule, essential for osteoclastogenesis, whose identity long remained enigmatic. In 1997, it was found that overexpression or administration of a protein, eventually termed osteoprotegerin (OPG), blunts osteoclastogenesis in mice. Similarly, animals lacking OPG have accelerated osteoclastogenesis and develop severe osteoporosis (*3*). OPG is now known to be a soluble "decoy" receptor that competes with RANK for RANKL (*4*). The presence of RANK on osteoclasts and their precursors (*4*) suggested that osteoclast-differentiating factor, residing on stromal cells, may be RANKL, which proved to be the case (*4*). RANKL is also expressed in abundance by activated T lymphocytes. These cells can directly trigger osteoclastogenesis and are probably pivotal to the joint destruction seen in rheumatoid arthritis (*5*). Indeed, it is the balance between the expression of the stimulator of osteoclastogenesis, RANKL, and of the inhibitor, OPG, that dictates the quantity of bone resorbed (*6*). Moreover, complete osteoclastogenesis can now be achieved in vitro with pure populations of macrophages exposed only to M-CSF and RANKL (*4*). The number of osteoclasts in these cultures can be modulated by varying the concentrations of these molecules. Thus, agents that induce M-CSF expression cause osteoclast precursors to proliferate. In fact, this may be a central pathogenetic mechanism in human osteoporosis (*7*). RANKL stimulates the pool of M-CSF–expanded precursors to commit to the osteoclast phenotype.

The importance of RANKL in osteoclast differentiation emphasizes the central role played by stromal cells and osteoblasts in the process. In fact, stromal cells and osteoblasts are the targets of most osteoclastogenic agents that exert their effect by enhancing RANKL expression and thus increasing the quantity of this molecule relative to that of OPG. One such agent is parathyroid hormone (PTH) (*8*). Disorders of excess PTH are characterized by accelerated osteoclastogenesis, yet osteoclasts lack high-affinity PTH receptors. PTH is now known to interact with receptors on osteoblasts and on certain stromal cells that produce the osteoclastogenic factor RANKL (*8*). Similarly, 1,25-dihydroxyvitamin $D_3$, the biologically active form of vitamin $D_3$, which was previously believed to exert its osteoclastogenic effect by directly promoting osteoclast precursor differentiation, probably acts by inducing stromal cell and/or osteoblast expression of RANKL (*9*).

RANKL and RANK are members of the tumor necrosis factor (TNF) and TNF receptor superfamilies, respectively. This observation is consistent with clinical data indicating that inflammatory lesions of bone are characterized by abundant osteoclast proliferation. Indeed, TNF is a potent osteoclastogenic agent and appears to mediate orthopedic implant loosening, a disorder accompanied by local secretion of TNF (*10*). Furthermore, systemic administration of bacterial lipopolysacharide, which is likely to be an important pathogenetic factor in the alveolar bone loss seen in periodontitis, prompts rapid osteoclastogenesis through the p55 TNF receptor (*11*). The p75 TNF receptor, by contrast, is anti-osteoclastogenic (*12*). Thus, the two TNF receptors may reciprocally regulate osteoclastogenesis. In keeping with the osteoclastogenic properties of RANK and the p55 TNF receptor, they induce similar intracellular signals. The two critical distal events are activation of NF-κB and c-Jun $NH_2$-terminal kinase (JNK).

The precise cellular target of TNF in osteoclastogenesis and its relationship to RANKL remain contentious issues. TNF stimulates osteoblastic cells to express RANKL (*13*) and M-CSF (*14*), which in turn prompt macrophages to become osteoclasts. Whether TNF, in the absence of RANKL, directly targets macrophages to induce their differentiation into osteoclasts is controversial, however. It is likely that TNF directly targets osteoclast precursors but must do so in the context of at least a small amount of RANKL. Consistent with this hypothesis, systemic administration of OPG blocks osteoclastogenesis in experimental arthritis, a situation in which there are abundant amounts of TNF (*5*).

Interleukin-1 (IL-1), like TNF, stimulates M-CSF expression by marrow stromal cells, and this effect is inhibited by estrogen (*14*). There is considerable evidence that the enhanced osteoclastogenesis attending postmenopausal osteoporosis reflects, at least in part, release of this inhibitory event, thus increasing ambient M-CSF (*14*). A more complete discussion of IL-1 and TNF in the pathogenesis of postmenopausal osteoporosis is discussed in the accompanying article by Rodan and Martin (*15*).

## How Do Osteoclasts Resorb Bone?

Bone resorption is a multistep process initiated by the proliferation of immature osteoclast precursors, the commitment of these cells to the osteoclast phenotype, and finally, degradation of the organic and inorganic phases of bone by the mature resorptive cells. At first approximation, the osteoclast resembles its relative, the foreign body giant cell, which is a macrophage polykaryon formed in response to exogenous particulate matter. The osteoclast is, however, more complex

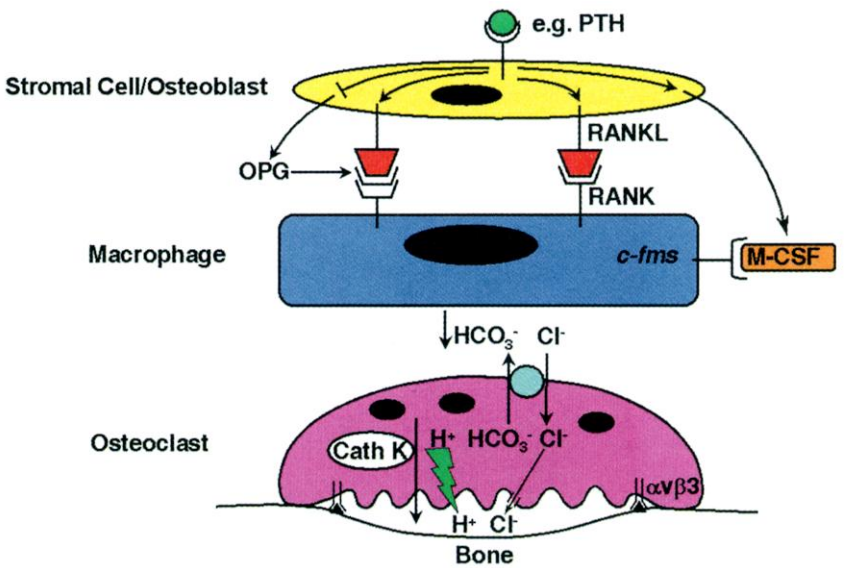


**Fig. 1.** Mechanisms of osteoclastogenesis and osteoclastic bone resorption. Stromal cells and osteoblasts express RANKL and M-CSF, which are up-regulated by osteoclastogenic molecules such as PTH. PTH also blunts expression of OPG. RANKL and M-CSF, interacting with their receptors on monocyte/macrophage cells, induce commitment to the osteoclast phenotype, a process inhibited by OPG. The differentiated osteoclast polarizes on the bone surface, which involves matrix-derived signals transmitted by the αvβ3 integrin. After formation of the ruffled membrane, the osteoclast acidifies an extracellular microenvironment by means of an electrogenic proton pump. Intracellular pH is maintained by $HCO_3^-/Cl^-$ exchange at the cell's antiresorptive surface. $Cl^-$ ions pass through a ruffled membrane-residing anion channel into the resorptive microenvironment, which achieves a pH approximating 4.5. The acidic milieu mobilizes the mineral phase of bone and provides an optimal environment for organic matrix degradation by cathepsin K.

and has a number of unique features that permit it to recognize and degrade bone. Most dramatic is the osteoclast's capacity to polarize on bone, and in so doing to form a "ruffled membrane." This complex infolding of the plasma membrane juxtaposed to the matrix is the osteoclast's resorptive organelle and appears only when the cell is attached to bone. The ruffled membrane probably represents the transport of acidifying vesicles along microtubules and their polarized insertion into the plasma membrane, an event similar to exocytosis (*16*, *17*). For example, the small guanosine triphosphatase Rab-3, which in other cells modulates the fusion of exocytic vesicles to the plasma membrane, may also regulate ruffled membrane formation (*18*).

The realization that the osteoclast is a member of the monocyte/macrophage family has prompted the development of techniques whereby macrophages, derived from many sources and at various stages of maturation, can be induced to differentiate into osteoclasts (*2*). Like their in vivo counterparts, these in vitro–generated osteoclasts are capable of bone resorption. When cultured on bone or dentin (another osteoclast substrate), osteoclasts excavate resorptive lacunae or "pits" that are similar to the structures formed when the cells degrade bone in vivo (Fig. 2). The number and size of resorption lacunae formed in vitro are a quantitative measure of osteoclast activity (*19*).

The initial event in bone degradation is the attachment of osteoclasts to the target matrix (Fig. 1). Once attached to bone, the cell generates an isolated extracellular microenvironment between itself and the bone surface (*20*). The intimacy between osteoclasts and bone, required for resorption, is reflected by the "matrix attachment" or "sealing" zone. This structure, rich in filamentous actin (F-actin) and largely devoid of organelles, is organized as a ring surrounding the ruffled membrane (*21*). The F-actin in the sealing zone localizes in punctate plasma membrane protrusions known as podosomes (*22*). In addition to F-actin, these structures contain proteins such as vinculin, talin, and α-actinin, which link matrix-recognizing integrins to the cytoskeleton (*23*). Whether the podosomal ring actually isolates the resorptive microenvironment from the general extracellular space, or serves as a matrix recognition structure by which integrins transmit extracellular-initiated signals prompting bone degradation, is unknown (*24*). The appearance of the podosomal ring, like the ruffled membrane, parallels bone resorption. The ring appears when the osteoclast is immobilized on and engaged in degrading bone and disappears after osteoclast detachment and motility (*21*).

Bone consists largely of type 1 collagen (>90%) and of noncollagenous proteins containing a mineral phase of substituted hydroxylapatite. Dissolution of the inorganic phase of bone precedes matrix degradation (*25*). Bone demineralization involves acidification of the isolated extracellular microenvironment, a process mediated by a vacuolar $H^+$–adenosine triphosphatase ($H^+$-ATPase) in the cell's ruffled membrane, which is similar to the proton pump in the intercalated cell of the renal tubule (*16*, *26*). It is possible, however, that one or more subunits of the osteoclast $H^+$-ATPase are unique to this cell (*27*). Again, as in the intercalated renal cell, the intra-osteoclastic pH is maintained, in the face of abundant proton transport, by an energy-independent $Cl^-/HCO_3^-$ exchanger on the cell's antiresorptive surface (*28*). Finally, electroneutrality is preserved by a ruffled membrane $Cl^-$ channel, charge-coupled to the $H^+$-ATPase (*29*). The result of these ion transporting events is secretion of HCl into the resorptive microenvironment, prompting a pH of ~4.5 (*20*). This acidic milieu first mobilizes bone mineral; subsequently, the demineralized organic component of bone is degraded by a lysosomal protease, cathepsin K (*27*, *30*). The products of bone degradation are endocytosed by the osteoclast and transported to and released at the cell's antiresorptive surface (*31*).

The role of metalloproteinases in osteoclast function is less clear. The most compelling evidence that these enzymes participate in the resorptive process comes from the demonstration that bone resorption is attenuated in mice carrying a mutation in the site in type 1 collagen that is targeted by neutral collagenases (*32*).

The functional cycle of the osteoclast consists of episodes of matrix adherence followed by detachment and movement to a new site of bone degradation (*21*). Although the events initiating bone resorption are reasonably well understood, less is known about the signals that arrest the process. A provocative argument holds that plasma membrane receptor sensing of high calcium levels within the resorptive space prompts the withdrawal of the osteoclast from the bone surface and the termination of resorption at that site. On the other hand, there is increasing evidence that the bone-sparing effects of antiosteoporosis agents such as estrogen (*33*, *34*) and bisphosphonates (*35*) reflect in part a stimulation of osteoclast apoptosis. In the case of estrogen, osteoclast death is mediated by transforming growth factor–β (TGF-β) (*33*), whereas bisphosphonates promote apoptosis by inhibiting the melavonate pathway (*35*).

As noted above, physical intimacy between matrix and cell is required for osteoclastic bone resorption, and it appears that the recognition of bone by osteoclasts is controlled by integrins. β1 integrins may participate by binding to type 1 collagen, but the major attachment molecule is αvβ3. Blocking studies using antibodies and competitive ligands (*36*) have established that the αvβ3 integrin is essential for bone attachment and resorption in vitro, and the $\beta3^{-/-}$ mouse confirms the same in vivo (*37*). Osteoclasts from these mutant mice do not form actin rings, have abnormal ruffled membranes, and fail to effectively resorb bone in vivo. Consistent with retarded bone resorption, αvβ3-deficient mice have low levels of blood calcium and increased skeletal mass.

Although the αvβ3 integrin is pivotal to the resorptive process, its most important function is probably not the formation of a physical seal between the osteoclast and bone. It most likely transmits bone matrix–derived signals, ultimately prompting intracellular events such as cytoskeletal organization (for example, formation of the ruffled membrane) that are pivotal to bone resorption (*37*). This putative function of the integrin is

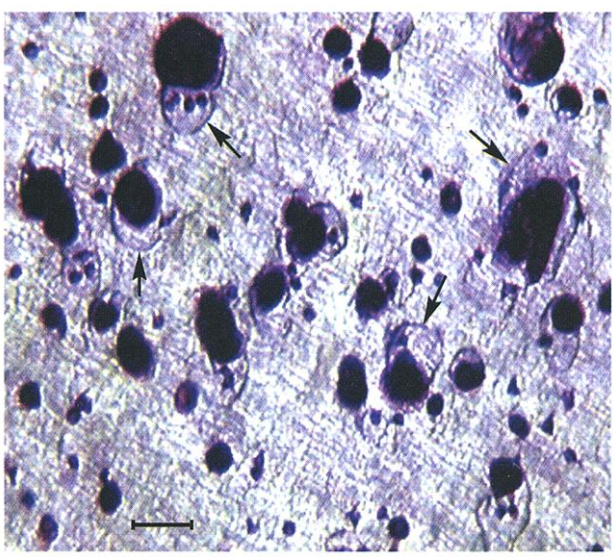

**Fig. 2.** Osteoclasts generated in vitro resorb dentin. Mouse bone marrow macrophages, placed on whale dentin (a resorptive substrate), were exposed to RANKL and M-CSF. After 6 days, the cells were stained for tartrate-resistant acid phosphatase activity (dark purple) reaction product. Although this enzyme is not unique to the osteoclast, it serves, in the framework of normal marrow, as the cell's most convenient marker. The macrophages differentiate into a homogeneous population of osteoclasts, most of which are found in lacunae (arrows) that they have excavated in the dentin. Scale bar, 50 μm (provided by Deborah Novack).

in keeping with its association, in the podosome, with signaling molecules such as c-Src (*38*) and the FAK-like kinase Pyk-2 (*39*), both of which are activated upon αvβ3 occupancy. Thus, αvβ3 may be an attractive target for anti-osteoporosis therapy (*36*).

Although much is known about the means by which osteoclasts degrade bone matrix, there is less information about its role in bone remodeling. This ever-occurring process in mammals begins with the appearance of osteoclasts. Whether osteoclasts recognize predetermined loci within bone, or whether the selection of remodeling sites is stochastic, is unknown. After the degradation of a "packet" of bone, thus forming a resorption lacuna, osteoclasts depart and are replaced by osteoblasts that, in young individuals, completely restore the previously resorbed bone. As an individual ages, the amount of bone deposited in resorption lacunae by osteoblasts is less than that previously removed by osteoclasts. It is this negative balance of osteoblastic, relative to osteoclastic, activity that is responsible for the universal loss of bone that occurs with age and that, when pronounced, eventuates in clinically significant osteoporosis. The factors that orchestrate the sequential appearance of osteoclasts and osteoblasts at bone remodeling sites are one of the great enigmas of bone biology.

## Genetic Regulation of the Osteoclast

Osteopetrosis is a family of diseases characterized by a marked enhancement of bone mass that, by definition, is caused by osteoclast dysfunction. (Increased bone mass due to stimulated osteoblast activity is known as osteosclerosis.) It was the serendipitous study of this disorder, rare in humans but a common phenotype in mouse mutants, that has pinpointed many of the gene products now known to regulate osteoclast precursor differentiation and the means by which the mature osteoclast degrades bone (Fig. 3). In experiments performed almost 30 years ago, the injection of normal spleen cells into osteopetrotic mice was found to cure the osteopetrotic phenotype, indicating that the osteoclast is of hematopoietic origin (*40*). Shortly thereafter, the hematopoietic origin of osteoclasts was established in humans (*41*). The latter involved the cure of an osteopetrotic female by transplantation of bone marrow derived from her brother. After transplantation, the rescued osteoclasts, but not the osteoblasts, contained the male chromosome, establishing that the osteoclast is of hematopoietic origin (coming from the donor in this case) and that its ontogeny differs from that of the osteoblast.

The osteoclast is derived from the monocyte/macrophage lineage (*2*), and it therefore follows that genes regulating the maturation of these mononuclear cells would also modulate the osteoclast. One example is the *PU.1* gene, which encodes a transcription factor essential for macrophage differentiation (*42*). Mice deficient in PU.1 lack not only macrophages but also osteoclasts, and they therefore develop osteopetrosis. Bone marrow transplantation, which provides normal osteoclast progenitors, is curative. The transcription factor c-Fos is also required for osteoclast differentiation. The deletion of c-Fos blunts expression of Fra-1, which like c-Fos is a member of the AP-1 transcription factor family. Inactivation of c-Fos in mice results in arrested osteoclastogenesis and osteopetrosis that can be rescued by marrow transplantation (*43*) as well as by a transgene expressing Fra-1 (*44*). In addition, c-Fos–deficient mice have elevated numbers of marrow macrophages (*43*). c-Fos therefore serves to commit hematopoietic precursors to become osteoclasts instead of mature macrophages, and it exerts its effect distal to PU.1, which is necessary for early macrophage maturation. The critical role of AP-1 transcription factors in osteoclast differentiation is underscored by the fact that overexpression in macrophages of another member of the family, c-Jun, mutated to render it nonactivatable by JNK, prevents their differentiation into osteoclasts (*45*).

The transcription complex NF-κB is also essential for osteoclastogenesis, because mice lacking its p50 and p52 subunits develop osteopetrosis caused by the arrested generation of osteoclasts from macrophages (*46*). Because the osteoclast precursor is defective in NF-$\kappa B^{-/-}$ mice, this form of osteopetrosis can also be cured by marrow transplantation.

RANKL (*47*) and M-CSF (*48*) are essential for osteoclastogenesis, and mice lacking either protein fail to generate osteoclasts and hence develop osteopetrosis. The cellular defect in these mutants, unlike other osteoclast-poor counterparts (namely, those deficient in PU.1, c-Fos, or NF-κB), lies not in the osteoclast precursor but in the stromal microenvironment necessary for osteoclastogenesis. Thus, the *op/op* osteopetrotic mouse, which carries a mutation in the *M-CSF* gene, is not cured by marrow transplantation (*48*) but responds to systemic administration of M-CSF (*49*). Osteopetrosis in the *op/op* mouse resolves spontaneously over time because of the progressive expression of granulocyte/macrophage colony-stimulating factor (GM-CSF) (*50*). M-CSF and GM-CSF are therefore redundant in osteoclastogenesis.

The essential role that the ruffled membrane plays in the osteoclast's bone resporptive activity is most dramatically illustrated by the c-Src–deficient mouse (*51*). This osteopetrotic mutant produces large numbers of osteoclasts that do not form ruffled membranes and hence fail to resorb bone (*52*). Thus, the skeletal dysfunction in the c-Src null mouse lies not in osteoclast recruitment but in the resorptive capacity of the mature osteoclast. The osteopetrosis in these mice is cured by marrow transplantation. This phenotype can also be partially rescued by a c-Src construct that is devoid of its kinase domain (*53*).

RANK, like other members of the TNF receptor superfamily, associates intracellularly with TNF receptor–associated factors (TRAFs). Mice lacking TRAF 6 have abundant dysfunctional osteoclasts and are osteo-

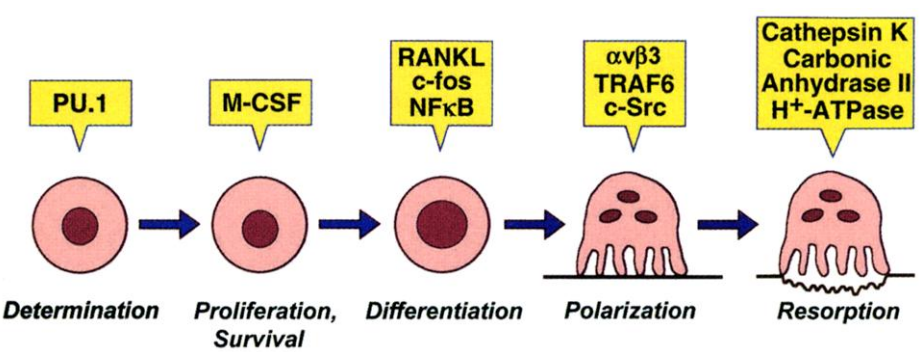


**Fig. 3.** Molecular mechanisms of osteopetrosis. The study of osteopetrotic mouse mutants provides insight into the genes regulating the sequential steps of osteoclast differentiation and function. PU.1 deficiency is lethal, because the mice have no early macrophage precursors. Although the number of macrophages is reduced, mice lacking M-CSF generate immature macrophages, and hence M-CSF exerts its effect later in the osteoclast differentiation pathway than does PU.1. c-Fos, NF-κB, and RANKL mutants show normal macrophage development, but the cell does not commit to osteoclast differentiation. Mice lacking the αvβ3 integrin, TRAF6, or c-Src have substantial numbers of osteoclasts, but the cells fail to adequately polarize, as manifested by the absence of a normal ruffled membrane. The cathepsin K, carbonic anhydrase II, and $H^+$-ATPase mouse mutants have osteoclasts that are morphologically normal but fail to resorb bone. Osteoclasts lacking carbonic anhydrase II or $H^+$-ATPase are incapable of acidifying the resorptive microenvironment between itself and bone, and osteoclasts lacking cathepsin K cannot degrade the organic matrix of bone.

petrotic (*54*). Given the central role of RANK in osteoclastogenesis and its use of TRAF 6 as an adapter molecule, this osteoclast-abundant phenotype is paradoxical, but it may reflect the fact that RANKL is needed not only for osteoclast differentiation but also for osteoclast activation (*55*). Finally, the absence of molecules necessary to degrade bone matrix, such as those regulating proton transport [$H^+$-ATPase (*27*) and carbonic anhydrase II (*56*)] or organic matrix degradation [cathepsin K (*30*)], results in morphologically normal osteoclasts that are incapable of effective resorption.

### Where Are We Going?

The past decade has witnessed a renaissance in osteoclast biology, due largely to the development of gene deletion technology and the capacity to generate this cell type in vitro. We now know that this polykaryon is central to the pathogenesis of postmenopausal osteoporosis and that the successes achieved thus far in preventing this disease reflect successes in decreasing osteoclast number and activity. A number of effective anti–bone-resorptive agents, such as estrogen, selective estrogen receptor modulators, and bisphosphonates, are in hand. Given our capacity to study the osteoclast both in vitro and in vivo, which will continue to provide new insights into its origin and function, new antiresorption drug targets are certain to emerge. Together with the promise of agents that are capable of stimulating bone formation, this offers real hope that effective prevention and reversal of osteoporosis are on the horizon.

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REVIEW

# Therapeutic Approaches to Bone Diseases

**Gideon A. Rodan[1]* and T. John Martin[2]†**

**The strength and integrity of our bones depends on maintaining a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts. As we age or as a result of disease, this delicate balancing act becomes tipped in favor of osteoclasts so that bone resorption exceeds bone formation, rendering bones brittle and prone to fracture. A better understanding of the biology of osteoclasts and osteoblasts is providing opportunities for developing therapeutics to treat diseases of bone. Drugs that inhibit the formation or activity of osteoclasts are valuable for treating osteoporosis, Paget's disease, and inflammation of bone associated with rheumatoid arthritis or periodontal disease. Far less attention has been paid to promoting bone formation with, for example, growth factors or hormones, an approach that would be a valuable adjunct therapy for patients receiving inhibitors of bone resorption.**

To carry out its functions, bone is continuously destroyed (resorbed) and rebuilt at about 1 to 2 million microscopic sites per adult skeleton. Resorption is carried out by hematopoietically derived osteoclasts and takes about 3 weeks per site, whereas the rebuilding of lost bone by osteoblasts, derived from bone marrow stromal cells, takes about 3 to 4 months. In young adults, bone destruction and formation are balanced, and bone mass is maintained in a steady state, which is influenced by mechanical usage (*1*) and possibly by central homeostatic factors (*2*). There are a number of diseases of bone that result from an imbalance between bone resorption and formation. After age 40, bone destruction begins to exceed bone formation, leading to local or systemic bone loss called osteoporosis. Osteoporosis is a major public health problem and, although it occurs most commonly in women as a result of estrogen deficiency after menopause, it is increasingly recognized that other causes exist and that there is a high incidence of osteoporotic fractures in older men. Large increases in bone resorption and loss of calcium from bone (hypercalcemia of malignancy) are skeletal complications associated with many cancers and with bone metastases of breast and prostate tumors. A number of therapeutic strate-

[1]Merck Research Laboratories, West Point, PA 19486, USA. [2]St. Vincent's Institute of Medical Research, Melbourne 3065, Australia.

*To whom correspondence should be addressed. E-mail: gideon_rodan@merck.com

†Visiting Research Scholar at Lilly Research Laboratories, Indianapolis, IN 46285, USA.