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Osteoprotegerin and inflammation

Abstract

RANK, RANKL, and OPG have well established regulatory effects on bone metabolism. RANK is expressed at very high levels on osteoclastic precursors and on mature osteoclasts, and is required for differentiation and activation of the osteoclast. The ligand, RANKL binds to its receptor RANK to induce bone resorption. RANKL is a transmembrane protein expressed in various cells type and particularly on osteoblast and activated T cells. RANKL can be cleaved and the soluble form is active. Osteoprotegerin decoy receptor (OPG), a member of the TNF receptor family expressed by osteoblasts, strongly inhibits bone resorption by binding with high affinity to its ligand RANKL, thereby preventing RANKL from engaging its receptor RANK. This system is regulated by the

calciotropic hormones. Conversely, the effects of RANKL, RANK, and OPG on inflammatory processes, most notably on the bone resorption associated with inflammation, remain to be defined. The RANK system seems to play a major role in modulating the immune system. Activated T cells express RANKL messenger RNA, and knock-out mice for RANKL acquire severe immunological abnormalities and osteopetrosis. RANKL secretion by activated T cells can induce osteoclastogenesis. These mechanisms are enhanced by cytokines such as TNF-alpha, IL-1, and IL-17, which promote both inflammation and bone resorption. Conversely, this system is blocked by OPG, IL-4, and IL-10, which inhibit both inflammation and osteoclastogenesis. These data may explain part of the abnormal phenomena in diseases such as rheumatoid arthritis characterized by both inflammation and destruction. Activated T cells within the rheumatoid synovium express RANKL. Synovial cells are capable of differentiating to osteoclast-like cells under some conditions, including culturing with M-CSF and RANKL. This suggests that the bone erosion seen in rheumatoid arthritis may result from RANKL/RANK system activation by activated T cells. This opens up the possibility that OPG may have therapeutic effects mediated by blockade of the RANKL/RANK system.

Full text

The receptor activator of NF-kappaB (RANK), RANK ligand (RANKL) and osteoprotegerin (OPG) has well established regulatory effects on bone metabolism. Links with the immune system are less known, but it seems to play a major role in modulating the immune system.

ROLE IN BONE RESORPTION

RANK is a membrane-spanning 616-amino acid polypeptide that comprises two regions, an extracellular N-terminal region that binds to the ligand and a cytoplasmic C-terminal region that ensures signal transduction in response to the activation produced by binding to the ligand [1]. RANK was identified as a dendritic surface receptor, indicating a potential role in modulating dendritic cell differentiation and survival, but it has also been identified as the intrinsic hematopoietic cell surface determinant required for differentiation and activation of the osteoclast [2]. RANK is expressed at very high levels on osteoclast progenitor cells [3]. Mice deficient in RANK are also osteopetrotic and lack osteoclasts.

RANK binds to RANK ligand, thus inducing bone resorption [3, 4]. RANKL (also known as OPGL or ODF), is a type II transmembrane protein of 317 amino acid residues. The N terminal region of the protein encodes a short intracellular domain, followed by a hydrophobic transmembrane domain. The C terminal region encodes the extracellular domain of RANKL [4]. RANKL is expressed chiefly by cells of the osteoblastic line. T lymphocytes are among the other cell types that express RANKL [4]. Cleavage of RANKL releases an active, soluble form. RANKL activates osteoclastic differentiation of murine and human hematopoietic progenitor cells, stimulates osteoclast activation, and prolongs the osteoclast lifespan [6]. *In vivo*, mice given RANKL show marked bone loss with hypocalcaemia, whereas RANKL knock-out mice fail to produce mature osteoclasts and develop osteopetrosis [7]. RANKL expression by osteoblasts is enhanced by agents that increase osteoclast development *in vitro*, including vitamin D3, IL-1, PGE2, and parathyroid hormone (these agents also decrease OPG expression by osteoblasts) [7]. Calciotropic hormones and cytokines may regulate bone resorption by modulating osteoprotegerin (OPG) and RANKL expression during bone remodelling.

OPG is a cytokine of 401 amino acids that belongs to the TNF receptor superfamily. Inhibition of bone resorption has been established as the main effect of OPG. OPG is not a membrane receptor but a secreted protein, with two functional domains. The N-terminal half contains four tandem, cysteine-rich repeat sequences that are characteristic of the ligand-binding domains of all members of this family. The C-terminal half of the protein has no distinct homologies to any known proteins and is involved in OPG homodimerisation following biosynthesis. The C-terminal domain binds to heparin and may be involved in localisation to the extracellular matrix [8]. OPG has been strongly conserved during evolution, with 94% homology between the rat and mouse proteins and 89% between the mouse and human proteins. In humans, OPG is strongly expressed in the lungs, kidneys, intestine, spleen, thymus, and heart. OPG is also found in osteoblastic cells, and the messenger RNA (RNAm) of OPG has been detected in dendritic cells and lymphocytes [9].

The OPG decoy receptor plays a central role in bone metabolism regulation by inhibiting osteoclast differentiation and activation [10] and by increasing osteoclast apoptosis [10, 11]. *In vitro* studies have shown that both native and recombinant OPG block the formation of osteoclast-like multinucleate cells and decrease the expression of osteoclast markers, namely, the calcitonin receptor,

integrin alpha upsilonn beta3, and tartrate-resistant acid phosphatase (TRAP). These effects are related only to the N-terminal part of the protein [8].

Transgenic mice with OPG gene overexpression have an increase in bone mass similar to that seen in mice with osteopetrosis (op/op) [12]. Administration of recombinant OPG increases tibial and femoral bone mass in normal mice and counteracts the bone loss related to oestrogen deprivation in ovariectomised mice. Transgenic mice with OPG deficiency ($OPG^{-/-}$) develop severe osteoporosis with low bone mineral density and multiple fractures [13, 14]. OPG is produced by osteoblasts, and its expression is regulated by growth factors and steroid hormones: TGF-beta and BMP-2, which promote osteoblast differentiation, can induce OPG expression; calciotropic agents (VITD3, PGE2, and hydrocortisone), which increase bone resorption, and decrease OPG expression by osteoblasts [8, 9]. Thus, OPG is an antagonist cytokine that downregulates osteoclast activation and development by sequestering its ligand, RANKL, which binds specifically and with high affinity to OPG. The result is inhibition of bone resorption [16-19] (Figure 1).

In pathology, where there is an increase in bone destruction caused by aberrant production and activation of osteoclasts as in myeloma, RANKL, RANK and OPG seem to play a important role: Pearse *et al.* [20] found alterations in expression of RANKL and OPG in myeloma patients. In the bone marrow of these patients, RANKL is expressed by stromal and activated T cells. In coculture, osteoclast development requires expression of RANKL by stromal cells and is blocked by addition of RANK. *In vivo* administration of RANK-Fc abrogates the development of bone disease in the SCID-Hu murine model of human myeloma [20]. Finally, *in vitro*, the constitutive stromal expression of OPG is reduced [20].

MODULATION OF THE IMMUNE SYSTEM BY RANKL, RANK, AND OSTEOPROTEGERIN

In addition to the regulatory effects of the RANKL/RANK/OPG system on bone remodelling, several arguments point to an interaction of this system with the immune response.

RANKL, RANK, and OPG seem to be involved in the immune response *via* effects on T cells and dendritic cells [21, 22]. RANK expression has been found on dendritic cells (DCs) and RANK activation by RANKL prevents apoptosis (by

increasing Bcl-xl), and increases the DCs lifespan, thereby causing proliferation of T cells (activated by DCs) [19, 22, 23]. OPG suppresses all these effects, decreasing the production of cytokines in response to DC stimulation by RANKL/RANK, *i.e.*, pro-inflammatory cytokines such as IL-6, IL-11, and cytokines produced by T cell proliferation (IL-12, IL-15) [23, 24]. RANKL and RANK are also indispensable in lymphoid tissue development. Mice deficient in RANKL or RANK develop severe immunological abnormalities secondary to abnormal development of B cells and thymocytes; also, their T cells do not respond appropriately to stimulation by DCs [21, 25]. Similarly, in addition to severe osteopetrosis, these animals have no lymph nodes, and their thymus and Peyer's patches are hypoplasic. Their spleen is enlarged, indicating extramedullary haematopoiesis [21-25]. Thus, the RANKL-RANK system is at the epicentre of two pivotal immune system functions:

1) early development and maturation of pre-B and pre-T cells in the marrow and thymus [25];

2) and interaction between T cells and mature DCs [25].

The involvement of the RANKL/RANK/OPG system in both bone resorption and immune responses suggests a role in the interactions between T cells and bone remodelling.

RANKL/RANK and T cells

Several studies found increased RANKL mRNA expression in activated T cells [26, 27]. RANKL induction may be dependent on protein kinase C [28]. RANKL expression occurs at the surface of activated, but not quiescent, murine T cells. It has also been shown that activated T cells secrete soluble RANKL into the culture medium (supernatant of CD4+ cells activated for four days by alphaCD3 and alphaCD28 cells [28]).

Kong *et al.* showed that both soluble and membrane-spanning RANKL produced by activated T cells induced osteoclastogenesis *in vitro*. They cultured hematopoietic precursors from mouse marrow either with $CD4^+$ T cells or with supernatants of $CD4^+$ T-cell cultures. In both cases, osteoclastic cells developed. This effect was specifically blocked by addition of OPG to the culture medium but persisted after addition of anticytokine antibodies [28]. When OPG

was present, the cytokines IL-1, IL-6, TNF, INF-gamma, IL-3, and GM-CSF failed to induce osteoclast development, suggesting that RANKL secreted by T cells may be the key factor in osteoclast development [28]. Thus, several lines of evidence indicate that T cells may act on bone resorption *via* a RANKL-mediated effect.

To evaluate the extent to which T-cell activation may affect bone remodelling *via* a RANKL-mediated effect *in vivo*, CTLA4$^{-/-}$ mice were studied. These mice are characterized by spontaneous T-cell activation and by severe osteoporosis. Another mouse line, rag1$^{-/-}$, lacks lymphocytes but has normal bone physiology. Grafting CTLA4$^{-/-}$ marrow cells into rag1$^{-/-}$ mice induced decreases in total and trabecular bone mineral densities as compared to controls. Histology showed severe bone resorption with an expanded osteoclast population. Furthermore, daily injection of RANKL to CTLA4$^{-/-}$ mice increased bone mineral density and decreased the number of osteoclasts [28]. Finally, a recent study in healthy volunteers showed that activated T-cells expressing RANKL can induce formation of osteoclast-like cells from peripheral blood mononuclear cells [29]. These findings show that *in vivo* T cell activation leads to bone loss *via* a RANKL-mediated effect.

Effect of immuno-inflammatory cytokines on the RANKL/RANK/OPG system

Further support for a link between the immune system and bone resorption comes from evidence that cytokines such as TNF-alpha, IL-1, IL-11, and IL-17, which regulate immune functions, are also involved in regulating bone homeostasis.

Many pro-inflammatory cytokines activate bone resorption (IL-1, IL-6, IL-11, IL-17, M-CSF, TNF-alpha, and PTHrp). These cytokines have been detected in the synovial membrane from patients with rheumatoid arthritis (RA) [30,-32]. There is evidence that they promote synovial inflammation and osteocartilaginous resorption by stimulating osteoclastic mediators [32, 33]. The key role of RANKL, RANK, and OPG in bone metabolism and immune function has generated the hypothesis that these cytokines and the RANK/RANKL/OPG system may act together to trigger bone resorption *via* regulation of the RANKL/OPG ratio. In support of this hypothesis, studies have shown that IL-1, IL-11, IL-17, TNF, PTHrp, and PGE2 increased RANKL mRNA expression by T cells and that both PTHrp and PGE2 decreased OPG expression [18, 34, 35]. The effect of IL-1 and TNF-alpha is less clear, since these compounds stimulate both RANKL and OPG. Furthermore,

these two cytokines can induce osteoclastic activation *via* a mechanism independent of RANKL [36, 37]. However, TNF dramatically stimulates differentiation in macrophages primed by less than one percent of the amount of RANKL required to induce osteoclast formation. Mirroring their synergistic effects on osteoclast differentiation, TNF and RANKL potentiate NFkappaB and stress-activated protein kinase c-Jun NH_2-terminal kinase activity. While TNF alone does not induce osteoclastogenesis, it does so both *in vitro* and *in vivo* by directly targeting macrophages within a stromal environment that expresses appropriate levels of RANKL [38]. IL-6 is a cytokine characterized by a strong resorptive effect and can induce formation of RANKL mRNA in cultures of stromal cells from rodent marrow but not from human marrow [37, 39]. IL-7 seems also to play a major role in the mechanisms underlying bone destruction. Mice respond to IL-7 injection by an increase in bone resorption [40]. Mice with a genetically-engineered change in the IL-7 receptor have a higher trabecular bone mass than normal [41]. IL-1 and TNF-alpha may cause stromal cells and osteoblasts to produce IL-7, which may in turn induce osteoclastogenesis *via* the RANKL system, independently of the presence of M-CSF [36, 40]. Finally, a study in humans suggests that IL-17 produced by activated T cells may play a major role in bone resorption *via* a RANKL-mediated mechanism [42]. Blocking of bone-derived endogenous IL-17 with specific inhibitors resulted in a protective inhibition of bone destruction. Conversely, intra-articular administration of IL-17 into a normal mouse joint, induced cartilage degradation [43].

T cells not only produce RANKL, they are also linked to bone metabolism *via* other cytokines. It is worth noting that some of these T-cell-derived cytokines, such as INF-gamma, IL-4, and IL-10, can inhibit osteoclast formation *in vitro* [30].

The effects of IL-12 and IL-18 are surprising. These two cytokines were initially described as INF-gamma-inducing agents and have been shown to act in synergy, with combined treatment resulting in far greater INF-gamma production than with either cytokine alone [44, 45-47]. In addition to their effect on INF-gamma, the combination of IL-12 and IL-18 has been shown to increase the proliferation and activation of T cells and NK cells [48-50] and to promote the Th1 response [51]. However, IL-18 is able to inhibit osteoclast formation *via* T cell production of GM-CSF, highlighting a role for cell types other than osteoblast in the regulation of osteoclastogenesis [52]. IL-12 can also inhibit osteoclast formation in mouse coculture and adult spleen cultures *in vitro*. This action is probably mediated by T-cells: IL-12 was able to inhibit osteoclast formation in M-

CSF - and RANKL - stimulated splenic cultures, although removal of T cells from these cultures rendered IL-12 ineffective. The exact mechanism is not known. Despite the known inhibitory action of INF-gamma on osteoclast formation *in vitro*, it is probably not the major intermediate in the inhibitory effect of IL-12 [53]. In cocultures using spleen cells and osteoblasts from INF-gammaR$^{-/-}$ mice, the complete ablation of osteoclast formation in response to IL-12 was still evident.

Hormonal regulation

Estrogen deficiency induces bone loss by upregulating osteoclastogenesis *via* mechanisms not completely defined. T cells expressing estrogen directly regulate T-cell function and cytokine production [54-56]. Moreover, T-cell subset alterations occur in women with post-menopausal osteoporosis [57, 58]. Taken together, these findings suggest that T cells may contribute to enhance osteoclast formation and induce bone loss not only during inflammation, but also in conditions of estrogen deficiency. Genci *et al.* [59] investigated the role of T cells in ovariectomy-induced bone loss. They reported that ovariectomy enhanced T cell production of TNF-alpha, which acts through the TNF-alpha receptor p55, and increased M-CSF and RANKL-induced osteoclastogenesis. They also showed that ovariectomy failed to induced bone loss, stimulated bone resorption and increased osteoclast formation in T cell-deficient mice, establishing T cells as essential mediators of the bone-wasting effects of estrogen deficiency *in vivo*. Because T cell-deficient mice have normal bone physiology and only a modest increase in bone mineral density, T cells are probably not required for normal bone remodeling. Reports have shown that TNF-alpha at high concentrations (> 20 ng/ml) promotes osteoclast formation independently of RANKL, through NFkappaB and Jun NH_2-terminal (JNK) activation [35, 36]. Activation of these two signaling patways is also responsible for the osteoclastogenic activity of RANKL. Thus it is likely that additive effects of RANKL and TNF-alpha on JNK and NFkappaB activation accounted for the observed potentiating effect of TNF-alpha and RANKL and M-CSF-induced osteoclastogenesis. Taken together, these observations provide a mechanism to explain how the small increase in T cell-produced TNF-alpha, induced by estrogen deficiency leads to increased osteoclast formation and bone loss. However, since TNF-alpha stimulates the production of both M-CSF and RANKL, it does not exclude the possibility that in conditions in which suboptimal levels of RANKL and M-CSF are present in bone marrow, an additional mechanism by

which T cell-produced TNF-alpha stimulates osteoclast formation is by increasing the production of these cytokines.

Molecular mechanism of action

Members of the tumor necrosis factor receptor (TNFR) super family are known to mediate important and diverse physiological functions, including apoptosis, osteoclastogenesis, and immune system regulation [3, 4, 60]. The specific biological outcomes governed by these cell surface receptors are dependent not only on stimulation by their cognate ligands but also on various cytoplasmic signal transducing proteins [60, 61]. TNFR-associated factors (TRAFs) have been implicated in mediating signals induced by a subset of TNFR family members, leading to the activation of NFkappaB [62, 63]. NFkappaB is a ubiquitously-expressed transcription factor that controls a plethora of genes, including those involved in regulating apoptosis, immune responses and embryonic development. Although the physiological roles of individual TRAF protein in CD40 signaling remain to be clarified, *ex vivo* data have suggested a potentially distinguished role for TRAF6. TRAF6 binds to a cytoplasmic domain of CD40, which is distinct from that containing the binding sites for the other TRAF protein [64]. Furthermore, the TRAF6-binding region is thought to be required for CD40-mediated NF-kappaB activation [64] IL-1 and LPS signaling [67]. In addition, TRAF6 plays a role in the regulation of bone metabolism: TRAF6-deficient mice exhibited osteopetrosis [65]. This deficiency seems to be linked more to a defect in osteoclast function rather than development. The osteopetrotic phenotype of $TRAF6^{-/-}$ mice have normal numbers of mature osteoclast that are impaired, with the formation of ruffled borders, and hence, do not resorb bone properly [66]. Some data argue against a role for TRAF6 in CSF-1 signaling, but the exact role during the osteoclast maturation and activation processes is not known. It is likely to involve signal transduction from an osteoclast surface receptor. A candidate signaling receptor is RANK. Most recently it was demontrated that multiple TRAF proteins including TRAF6 can interact with the carboxyl terminus of RANK [67].

Additional insight has been gained recently into the molecular mechanisms underlying RANKL-mediated effects of T cells. Interferon-gamma (INF-gamma) seems to play a crucial role. Bone destruction is increased in mice who have no receptor for INF-gamma (INFgamma-$R^{-/-}$), suggesting a key role for INF-gamma in bone remodelling [68]. In co-cultures of marrow cells and T cells from mice,

the interferon secreted by the T cells caused a decrease in osteoclast formation *via* a RANKL-dependent effect, but had little influence on marrow cell proliferation and survival, which depend on M-CSF, suggesting that INF-gamma may selectively interfere with the signal generated by RANKL.

The INF-gamma signal is transmitted through the Stat1 transcription factor. Its active form, INF-gamma-activated factor (GAF), induces the response of the interferon target gene, either directly or through induction of another transcription factor, IRF-1. However, the GAF-mediated pathway seems preponderant for the signal generated by RANKL. Stimulation by RANKL of its receptor RANK induces recruitment of proteins belonging to the TRAF family [69], and activates the pathway involving the NFkappaB and Jun N-terminal transcription factors. Among these proteins, TRAF-6 probably plays a major role: TRAF-$6^{-/-}$ mice develop osteopetrosis, with complete absence of osteoclasts. INF-gamma prevents RANKL from activating these transcription pathways by inhibiting TRAF-6 expression in a fairly selective manner (Figure 2). However, INF-gamma alone has no effect on TRAF-6: RANKL must be present also. Furthermore, TRAF-6 can be degraded only after ubiquitination. Although this process is initiated by RANKL, activation of the ubiquitin/proteasome system is also dependent on INF-gamma. Thus, interactions seem to occur between INF-gamma and RANKL, with a balance between these two compounds in which a preponderance of RANKL induces an increase in osteoclastogenesis. Consequently, T cells may regulate bone resorption by secreting either RANKL when they are activated or INF-gamma when they are not activated [30], during inflammation, which explains why bone loss is not more common than it is [70].

RHEUMATOID ARTHRITIS AND OSTEOPROTEGERIN

Local or general bone loss has been reported in several inflammatory diseases (hepatitis, HIV infection, leukaemias, autoimmune disorders, allergies, and rhumatoid arthritis (RA)), lending further weight to the hypothesis that immune system activation may affect bone physiology [70, 71].

RA is characterized by gradual joint destruction caused by chronic inflammation. The mechanism underlying the cartilage and bone destruction is poorly understood but may be mediated in part by proteinases such as metalloproteinases released by activated synovial cells, and by chondrocytes [39, 42]. However, recent studies suggest that osteoclasts may play a major role

in the bony erosions seen in patients with RA [42, 71-74]. In this disease, that combines inflammation and bone destruction, interactions between the OPG system and T cells may explain part of the abnormal phenomena.

In collagen-induced arthritis in mice, TRAP-positive multinucleate cells have been identified at the junction between the synovial pannus and the bone [75-77]. These cells have been found in the tibial diaphysis of rats after induction of adjuvant arthritis. It has been shown recently that these cells exhibit osteoclastic markers (TRAP expression, vibronectin receptor, calcitonin receptor, and the ability to form resorption bays on bone). Furthermore, they form within the synovial tissue, *i.e.*, at a site devoid of osteoblasts. This suggests that the rheumatoid synovium contains both osteoclastic precursors and the cells capable of inducing differentiation of those precursors [72, 73].

Osteoclasts can differentiate from the monocyte-macrophage line [70] in the absence of marrow hematopoietic cells. Furthermore, *in vitro*, synovial macrophages can differentiate to osteoclast-like cells in the presence of synovial fibroblastic cells [72-74]. Synovial macrophages from RA patients can differentiate to osteoclasts in the presence of M-CSF and RANKL [76]. RANKL is probably a key player in this differentiation process. RANKL is expressed in the synovial membrane at the sites where bone erosions develop, which also contain the RANKL receptor RANK [74, 75]. Conversely, RANKL is not found in normal synovial membrane, suggesting that RANKL mRNA may be associated with the synovial membrane abnormalities seen in RA [74].

Activated T cells comprise most of the cell population present in the rheumatoid synovium. These cells express RANKL and can induce formation of functional osteoclasts [26, 42, 71]. In adjuvant arthritis in Lewis rats, the lesions are dependent on T cell activation. It has been shown that RANKL is expressed at the surface of activated T cells isolated from rats with clinical evidence of incipient arthritis, and RANKL mRNA can be detected in the synovial cells and inflammatory infiltrate cells by *in situ* hybridisation. A seven-day course of OPG early in the disease prevents bone loss, whereas severe cartilage and bone destruction occurs in the untreated rats. Conversely, there is no effect on the severity of the clinical inflammatory manifestations. Thus, T cell activation can regulate bone resorption *via* the OPG/RANKL system in rats with arthritis [28].

The second source of RANKL in the synovial membrane is probably the population of synovial fibroblasts, stimulated by a host of cytokines. During adjuvant arthritis, the synovial fibroblasts and inflammatory cells express RANKL at a high level. Within seven days, cortical and trabecular bone loss develop, the osteoclast population expands, and the number of bone erosions increases [28].

Fibroblasts from rheumatoid synovium cultured with peripheral blood mononuclear cells induce osteoclastogenesis in the presence of $1,25(OH)_2D3$, and the surface cells then show a high level of RANKL expression, whereas OPG production in the supernatants of these cells is markedly reduced [69, 70, 72]. Adding OPG inhibits osteoclast formation in this culture model [73].

In patients with RA, *in situ* hybridisation and immunohistochemistry studies have identified RANKL on T cells within abnormal synovial membrane from RA patients, but not within synovial membrane from normal joints or joints with osteoarthritis [73]. Osteoclasts have also been found at sites characterized by the highest levels of RANKL expression, namely the junction between the synovial pannus and the bone [77-79].

Finally, OPG levels within the joint fluid seem lower in patients with RA than in patients with other patterns of arthritis responsible for less severe destruction [80].

These arguments suggest that T-cell activation may lead to the formation of osteoclasts within the synovial membrane. This effect probably involves secretion of RANKL by the activated T cells, which makes the microenvironment favourable to osteoclastic differentiation from synovial macrophages. This may explain part of the bone destruction seen in patients with RA (Figure 3).

PERSPECTIVES

The increase in bone resorption induced by elevation of the RANKL/OPG ratio opens up the possibility that recombinant OPG may have beneficial effects in several disorders. This is particularly exciting as recombinant OPG seems to have an excellent safety profile [81]. A recent study in postmenopausal women support to this possibility: OPG reduced bone resorption, with one monthly

injection producing an 80% reduction in the bone resorption marker deoxypyridinoline [81]. Furthermore, the safety profile was good [81].

In RA, OPG may become a new therapeutic weapon capable of combating both the inflammation and the bone resorption. In rats given OPG, Kong *et al.* found a decrease in bone resorption but not in inflammation, indicating that RANKL blockade by OPG did not interfere in this model with a T-cell-dependent immune and inflammatory response [28]. In mice with collagen-induced arthritis, administration of IL-4 to suppress RANKL and IL-17 expression by synovial cells, seemed to prevent the development of joint erosions [82]. A recent study suggests that neutralizing IL-1, TNF-alpha, and RANKL, by administering the IL-1 receptor, the soluble TNF receptor and OPG, eliminated both evidence of inflammation and bone loss in a rat model of adjuvant arthritis [83].

Thus, the RANKL/RANK/OPG system is at the core of the abnormal phenomena that characterize RA. This system may be partly responsible for the periarticular bone loss seen in this condition. However, much work remains to be done, in particular to elucidate the exact mechanisms of action and the relations that may exist between the RANKL/RANK/OPG system and the inflammatory response. There is good reason to hope that this will lead to more appropriate and less aggressive treatments.

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Figures

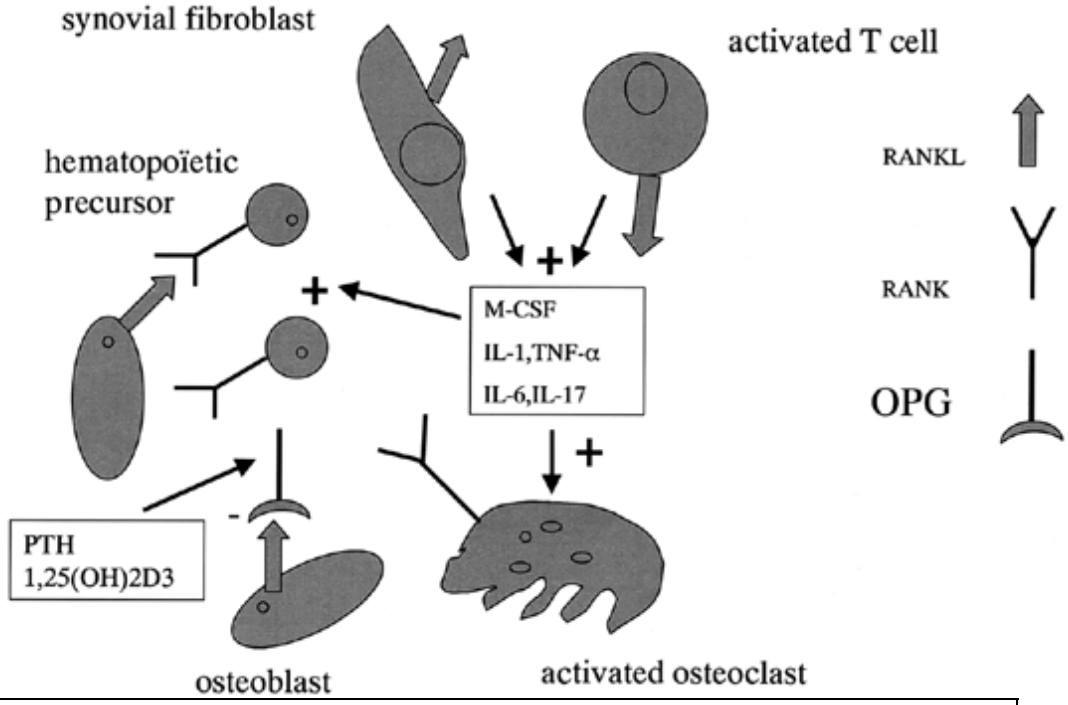


Figure 1

Interaction between membrane-bound RANKL on osteoblast bone stromal cells and its receptor RANK on osteoclast precursor cells.

This interaction leads to the differenciation of osteoclast precursor cells and the activation of osteoclast to resorb bone. OPG inhibits this interaction by binding to RANKL and blocking RANKL-RANK interaction.

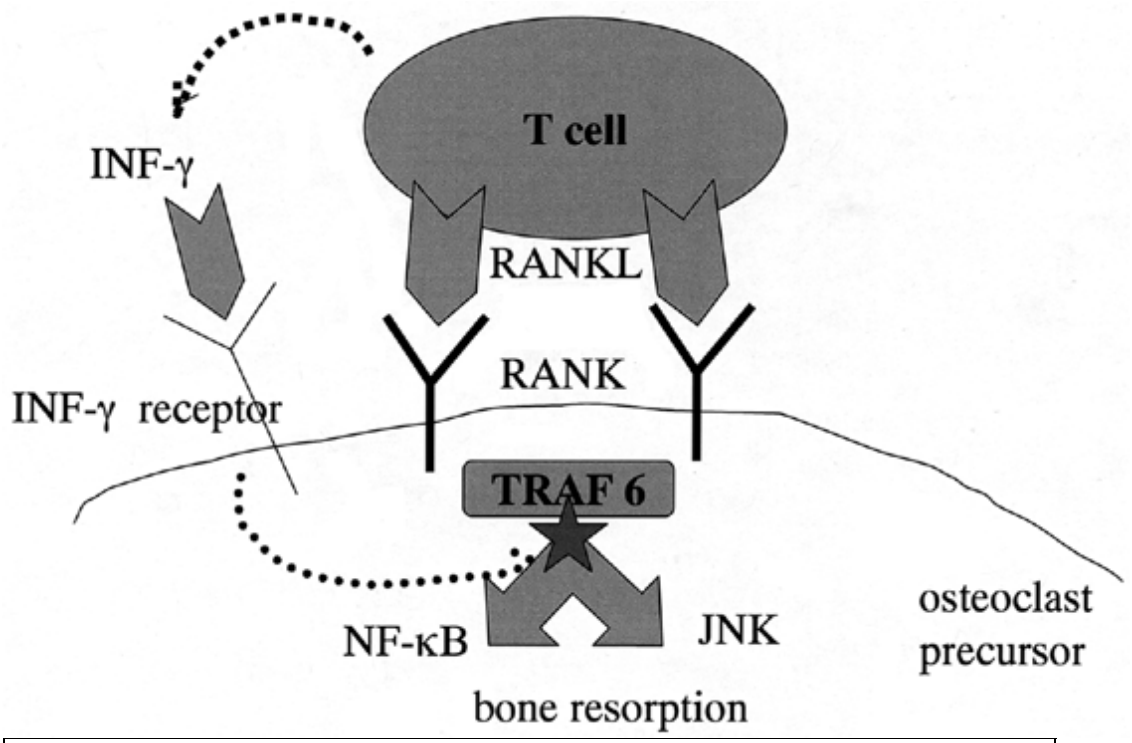


Figure 2

RANK signaling patway: RANK type I transmembrane protein on the cell surface in relation to cytoplasmic factors involved in RANK signal transduction.

RANKL binding to RANK induces the recrutment of TRAF protein and activation of NFkappaB and JNK. TRAF6 has been implicated as the major signal transducing TRAF protein involved in regulated osteoclastogenesis. Although the T cells involved in inflammatory conditions express RANKL, they also secrete INF-gamma. INF-gamma inhibited this signaling but in presence of RANKL suggesting interactions between RANKL and INF-gamma in osteoclastogenesis, to prevent activated T cells from triggering massive bone destruction during inflammation.

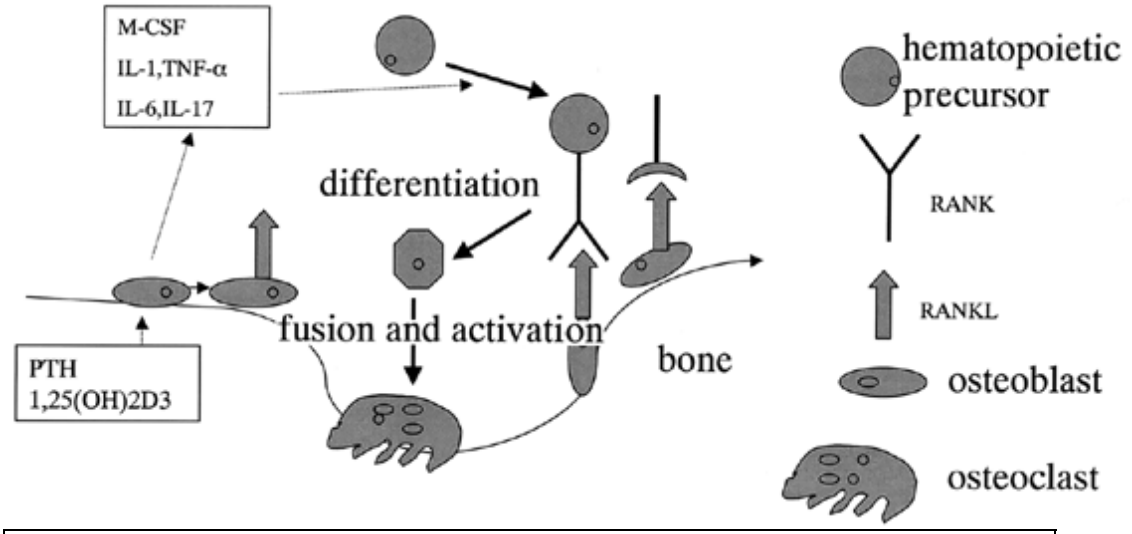


Figure 3

Mechanisms of bone resorption in rhumatoid arthritis.

Activated T cells express proinflammatory cytokin and RANKL. Synovial fibroblast and osteoclast also express RANKL which interact with its specific receptor RANK to promote osteoclast differentiation and activation, resulting in bone and cartilage destruction. This effects are counteracted by OPG, which is decreased in the synovial fluid of arthritis patients.

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Thioredoxin specifically cross-desensitizes monocytes to MCP-1

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