

Bone remodelling:

The skeleton is constantly undergoing remodelling: old bone is being replaced by new bone. Normal bone remodeling cycle requires that the process of bone resorption and bone formation take place in a coordinated fashion, which in turn depends on the orderly development and activation of osteoclasts and osteoblasts, respectively.

Bone remodelling is accomplished by bone resorption followed by new bone formation.

Once **osteoclasts** have resorbed a cavity of bone, they detach from the bone surface and are replaced by cells of the **osteoblast** lineage which in turn initiate bone formation. The osteoblasts fill the resorption cavity by laying down matrix that later becomes mineralized.

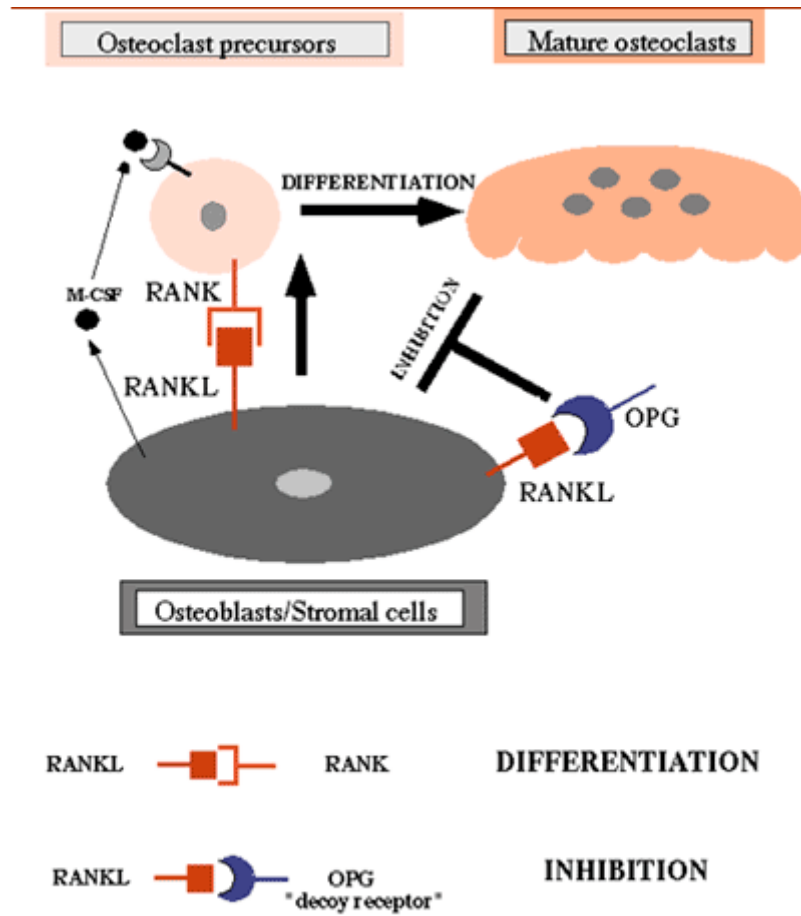
When the cycle is completed, the amount of bone formed should equal the amount of bone resorbed.

The complex series of events of bone remodelling are under the regulation of local factors.

1. Characteristics of Osteoprotegerin

The morphogenesis and remodelling of bone requires the synthesis of bone matrix by osteoblasts and its coordinated resorption by osteoclasts. Osteoprotegerin (OPG) also known as Osteoclast inhibiting Factor (OCIF) or Osteoclast Binding Factor (OBF), is a key factor inhibiting the differentiation and activation of osteoclasts, and is therefore essential for bone resorption. Osteoprotegerin is a dimeric glycoprotein belonging to the TNF receptor family with a molecular weight of 120 kD. As a so called soluble "decoy" receptor Osteoprotegerin inhibits the binding of RANK to RANKL and thus inhibits the recruitment, proliferation and activation of osteoclasts. In adult humans OPG/OCIF mRNA is highly expressed in various tissues e.g. heart, lung, kidneys, bone, liver, placenta, brain.

Abnormalities in the balance of OPGL/RANK/OPG system lead to the increased bone resorption that underlies the bone damage of postmenopausal osteoporosis, Paget's disease, bone loss in metastatic cancers and rheumatoid arthritis.



Molecular interaction of ligands and their receptors in the regulation of osteoclasts and their role in bone metabolism

2. Indication:

- Postmenopausal and senile osteoporosis
- Glucocorticoid-induced osteoporosis
- Diseases with locally increased resorption activity
- Therapy monitoring after treatment with OPG
- Arthritis
- Oncology

3. Biological effects of OPG

a) *Genetic models:*

Overexpression of OPG in transgenic mice:

Overexpression of OPG resulted in early, progressive osteopetrosis at various skeletal sites. Histologically, a systemic increase in mineralized trabecular bone was noted in mice overexpressing OPG.

Overexpression of OPG increased bone mass, mainly by inhibiting the terminal stages of osteoclast differentiation.

Deletion of OPG in knock-out mice:

Studies demonstrated that OPG knock-out mice develop severe, early onset osteoporosis.

Histologically, the bones of OPG deficient mice were markedly osteoporotic and almost completely lacked trabecular bone after 2 months of life.

b) *Exogenous administration of OPG*

In vitro effects of OPG

The major effects of OPG include inhibition of the terminal stages of osteoclastogenesis from osteoclast precursors and the activity of mature osteoclasts.

In vivo effects of OPG

Treatment of mice with daily subcutaneous injections of recombinant murine OPG resulted in a threefold increase in the trabecular bone mass.

In addition, the administration of recombinant murine OPG following ovariectomy increased bone volume and decreased osteoclast number, suggesting that OPG prevented estrogen deficiency-induced osteoclastic bone resorption.

4. Clinical Studies:

Animal models:

OPG blocks behaviours indicative of pain in mice with bone cancer. Treatment of OPG blocks cancer-induced skeletal destruction, skeletal pain, and pain-related neurochemical reorganisation of the spinal cord.

These clinical studies thus show that

OPG has a high potential for the treatment of osteoporosis and bone tumour associated pain.

Humans:

A first clinical study in post menopausal women confirms the potent and sustained anti-resorptive activity of OPG

Further clinical studies show that the expression of OPG depends on age and adequate estrogen supply.

Other metabolic diseases in which the OPG system may be involved in mediating increased bone resorption of in which exogenous administration of OPG may be potentially useful include:

- humoral hypercalcemia of malignancy
- rheumatoid arthritis-
- primary hyperparathyroidism

5. Osteoprotegerin Immunoassay

OSTEOPROTEGERIN ELISA (BI-20402)

Assay Characteristics:

Method: Sandwich ELISA, antibody coated strips

Sample: Human serum, EDTA-Plasma, Heparin Plasma,
cell culture supernatants

Sample volume: 50µl/test

Standard range: 0 - 30 pmol/l

Conversion factor pg/ml to pmol/l = 0.05 pmol/l (MW: 19.9 kD)

Incubation time: overnight/1h/20 min

Detection limit: (0 pmol/l + 3SD) 0.14 pmol/l

Precision: Intra-Assay <10%
Inter-Assay <10%

Storage: 4°C