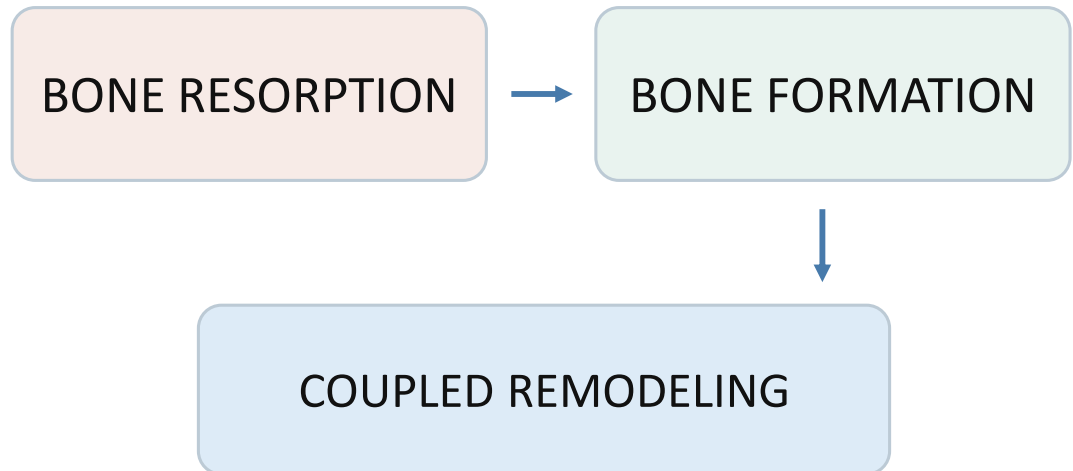


Homeostasis and Remodeling

Cellular coordination • Molecular signals • Skeletal mass



Schematic: sequential local remodeling

How removal and replacement remain coupled

Dr. Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Identify the cells and matrix participating in turnover
- Trace the bone multicellular unit (BMU) sequence
- Explain RANKL–RANK–OPG, M-CSF, and Wnt signaling
- Predict how systemic signals change the remodeling balance

Schematic

Cellular players

BMU sequence

Local signals

Systemic inputs

The skeleton is an active organ

Schematic

- An apparently static structure undergoes continuous renewal
- Bone provides mechanical support and force transmission
- Mineral storage and marrow support make remodeling physiologically consequential

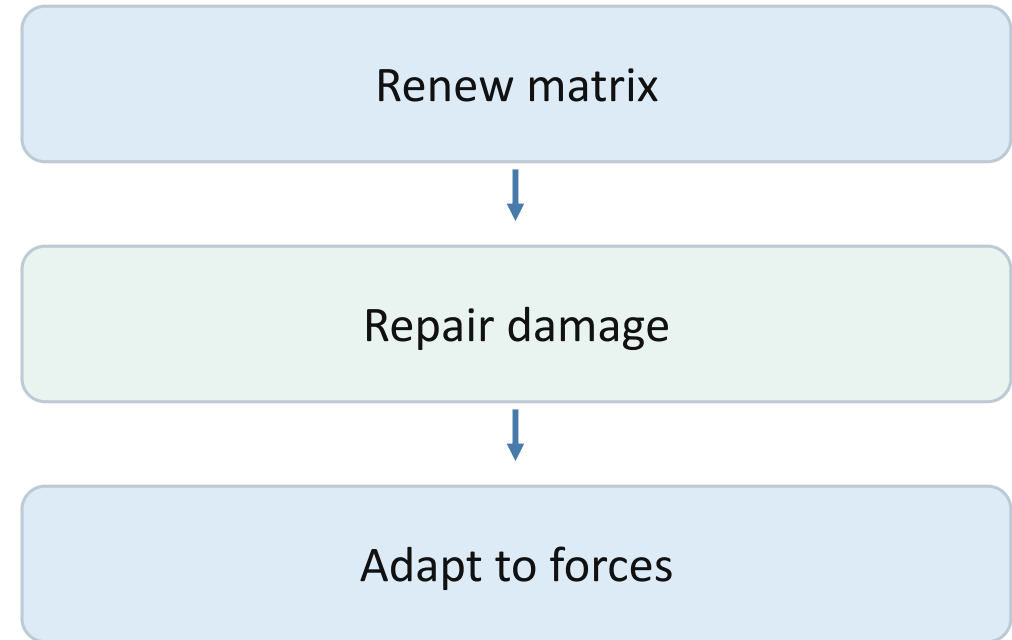
Mechanical role

Biological role

Why bone must be renewed

- Remodeling repairs microscopic damage
- Tissue architecture can adapt to mechanical loading
- Resorption and formation preserve the bone matrix over time

Schematic



Matrix combines a protein scaffold with mineral

- Osteoid constitutes approximately 35% of bone matrix
- The mineral component constitutes approximately 65%
- These components jointly determine material properties

Schematic

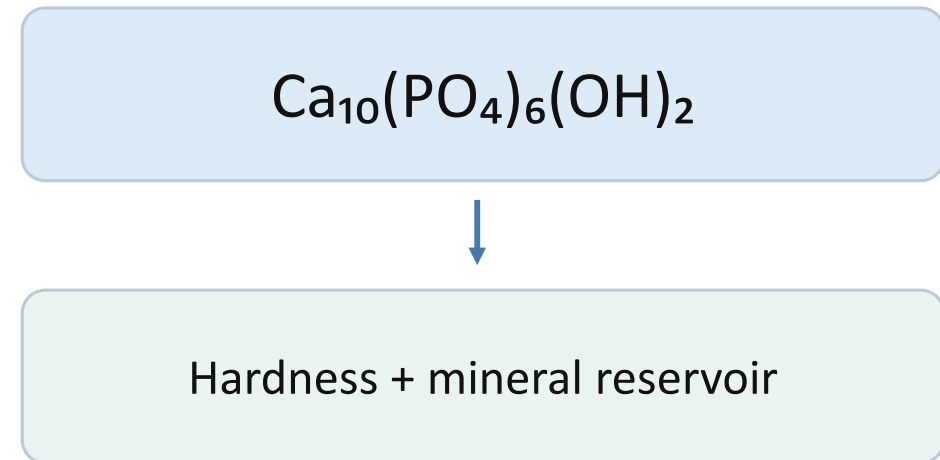


Textbook approximate matrix composition

Hydroxyapatite provides hardness

Schematic

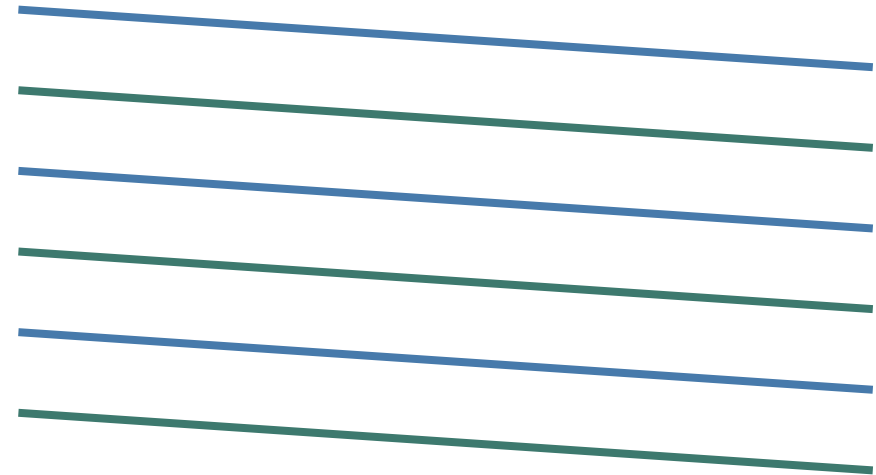
- The major mineral is hydroxyapatite:
 $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$
- Bone contains approximately 99% of body calcium
- Bone also stores approximately 85% of body phosphorus



Osteoid is predominantly type I collagen

- The organic framework is formed mainly by type I collagen
- Glycosaminoglycans and other noncollagen proteins are present
- Osteoblasts produce and organize this matrix

Schematic



Schematic: Collagen-rich osteoid framework

Osteocalcin links matrix and osteoblast activity

Schematic

- Osteocalcin is produced by osteoblasts
- It contributes to formation, mineralization, and calcium homeostasis
- Serum osteocalcin can serve as a marker of osteoblast activity

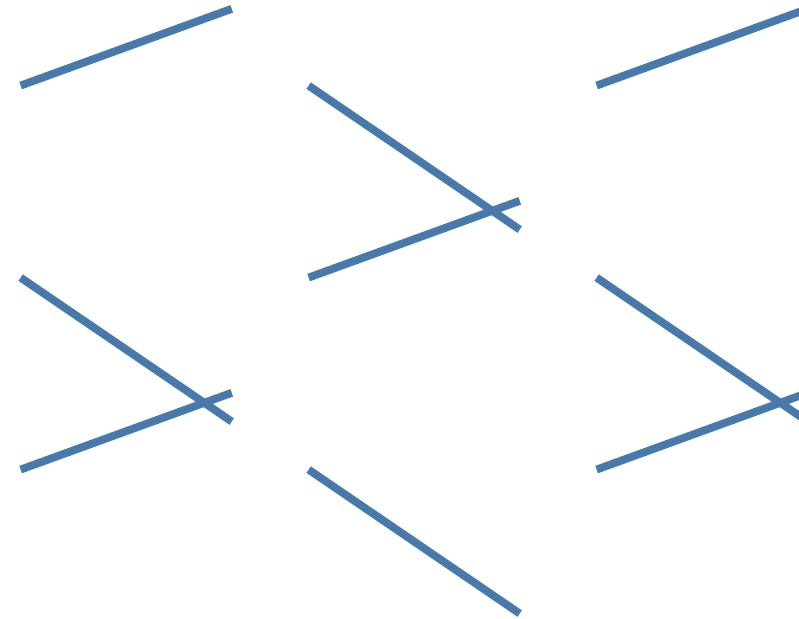
Mechanical role

Biological role

Woven bone favors speed over organization

- Rapidly deposited matrix has haphazard collagen orientation
- This irregular architecture gives less structural integrity
- Woven bone appears during fetal development or fracture repair

Schematic



Schematic: Non-parallel collagen arrangement

Lamellar bone favors organized strength

- Lamellar bone has more orderly, parallel collagen bundles
- It contrasts with disorganized and relatively cellular woven bone
- Maturation converts rapidly formed matrix into stronger architecture

Schematic

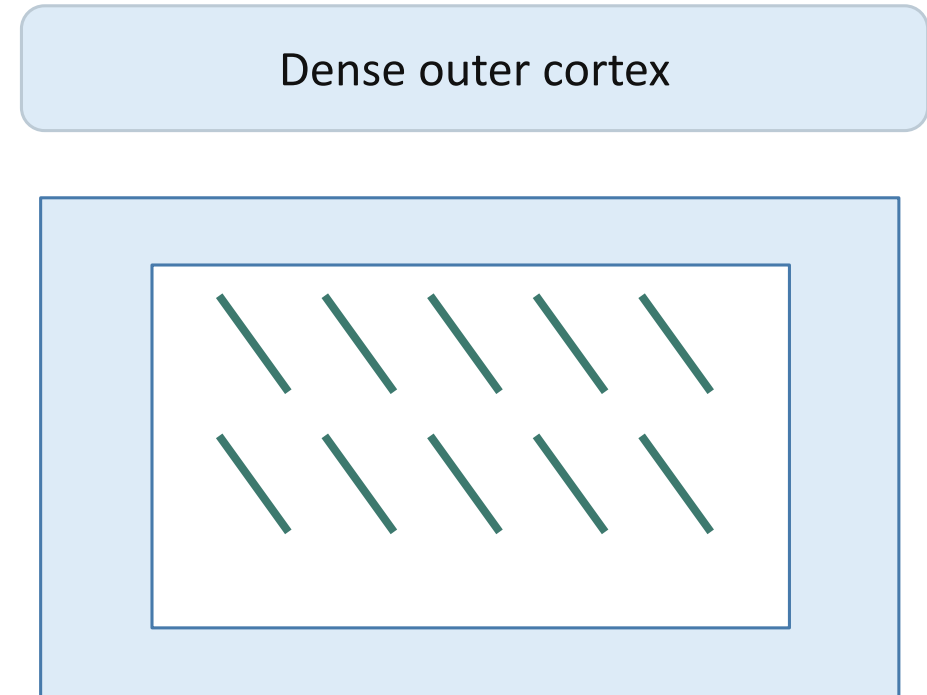


Schematic: Ordered, near-parallel lamellae

Cortical and trabecular compartments differ

- Dense cortical bone forms the outer shell of long bones
- Trabeculae support the central medullary space
- Marrow between trabeculae may be fatty or hematopoietic

Schematic



Schematic: Medullary cavity contains trabeculae and marrow

Three cell types perform distinct tasks

- Osteoblast: Produces and mineralizes osteoid
- Osteocyte: Senses forces and regulates the microenvironment
- Osteoclast: Removes preexisting bone

Schematic

OSTEOBLAST

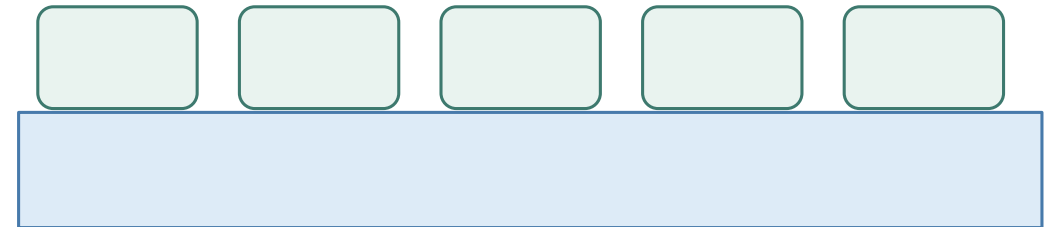
OSTEOCYTE

OSTEOCLAST

Osteoblasts construct the organic matrix

- Surface osteoblasts synthesize, transport, and assemble osteoid
- They regulate mineral deposition in the new matrix
- Their activity responds to hormones and local mediators

Schematic

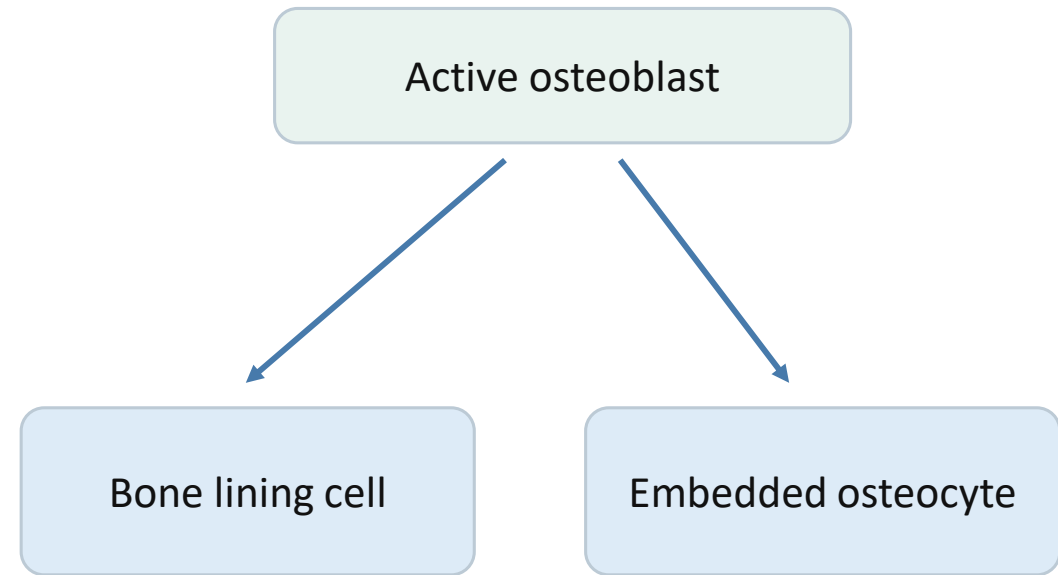


Schematic: Osteoblasts lining an osteoid surface

Osteoblast fate includes a resting state

- Quiescent osteoblasts have relatively scant cytoplasm
- Some remain as lining cells on the bone surface
- Others become embedded in matrix and differentiate into osteocytes

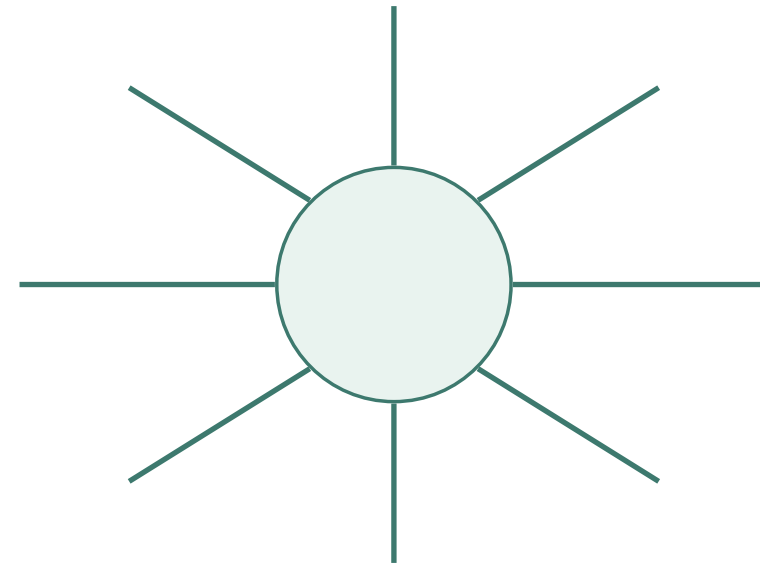
Schematic



Osteocytes form a communicating network

- Embedded osteocytes extend dendritic cell processes
- Processes communicate through microscopic canaliculi
- The network senses the tissue microenvironment

Schematic

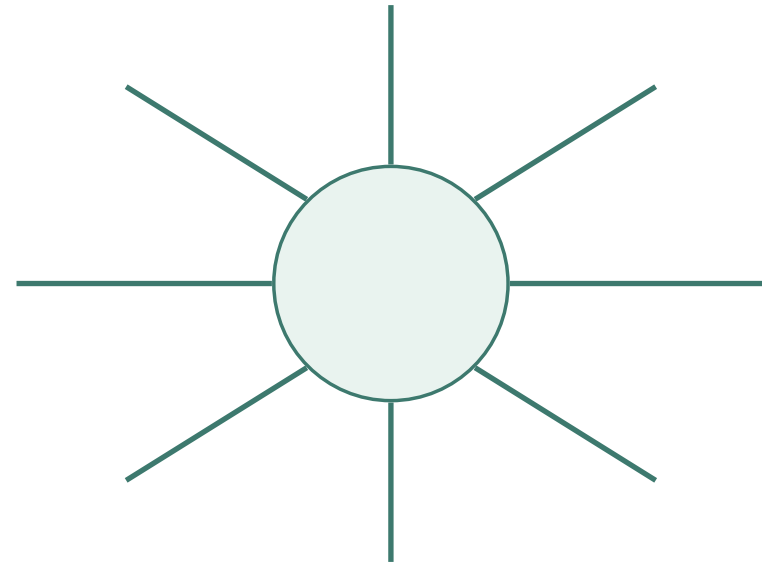


Schematic: Canalicular osteocyte connections

Osteocytes transduce mechanical forces

- Mechanical loading is detected by osteocytes
- Mechanotransduction converts physical input into biological signals
- This provides a cellular mechanism for load-responsive remodeling

Schematic

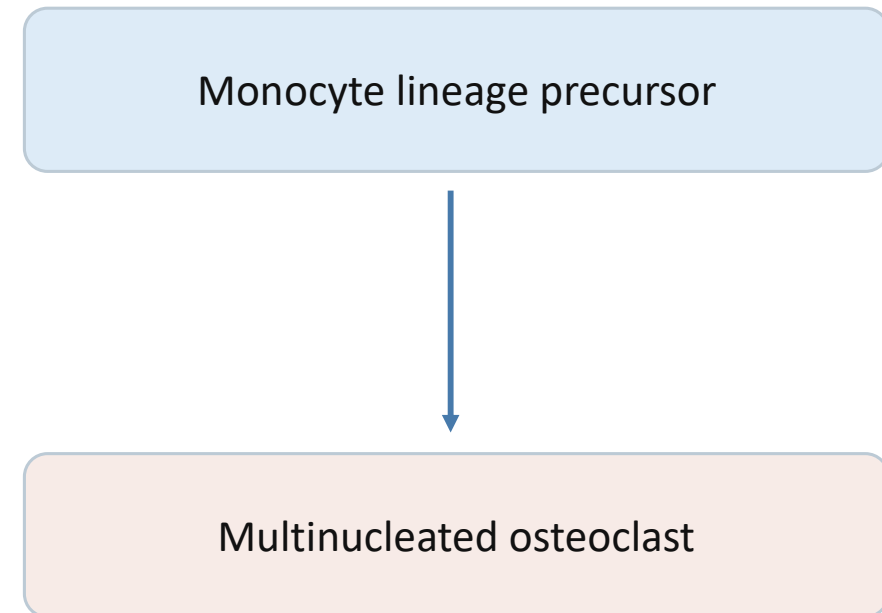


Schematic: Force sensing by osteocyte processes

Osteoclasts originate from monocyte-lineage cells

- Osteoclasts are multinucleated bone-resorbing cells
- They derive from circulating monocyte precursors
- Differentiation depends on signals supplied by bone-forming/stromal cells

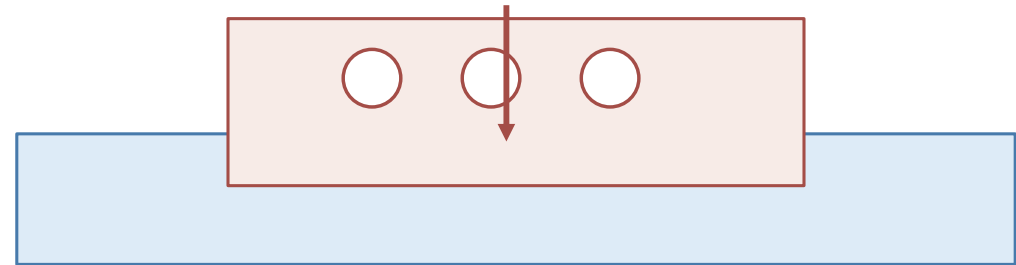
Schematic



Osteoclast attachment creates a resorption pit

- Cell-surface integrins mediate attachment to the bone matrix
- A locally sealed compartment forms between cell and bone
- The compartment focuses resorptive molecules at one site

Schematic

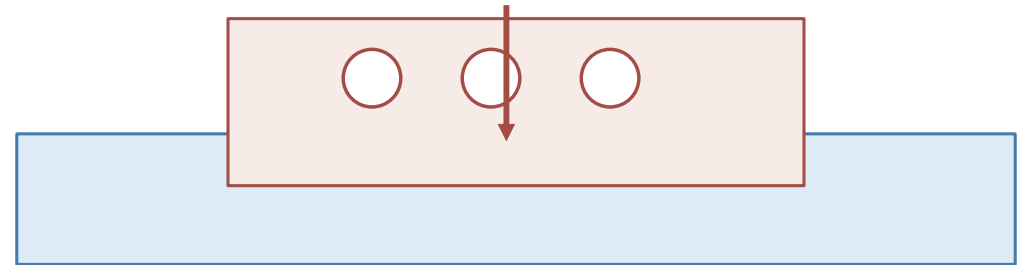


Schematic: Osteoclast over a sealed resorption site

Osteoclasts dissolve both matrix components

- Secreted acid dissolves the mineral component
- Proteolytic enzymes degrade the organic phase
- Matrix metalloproteases are among the enzymes described

Schematic

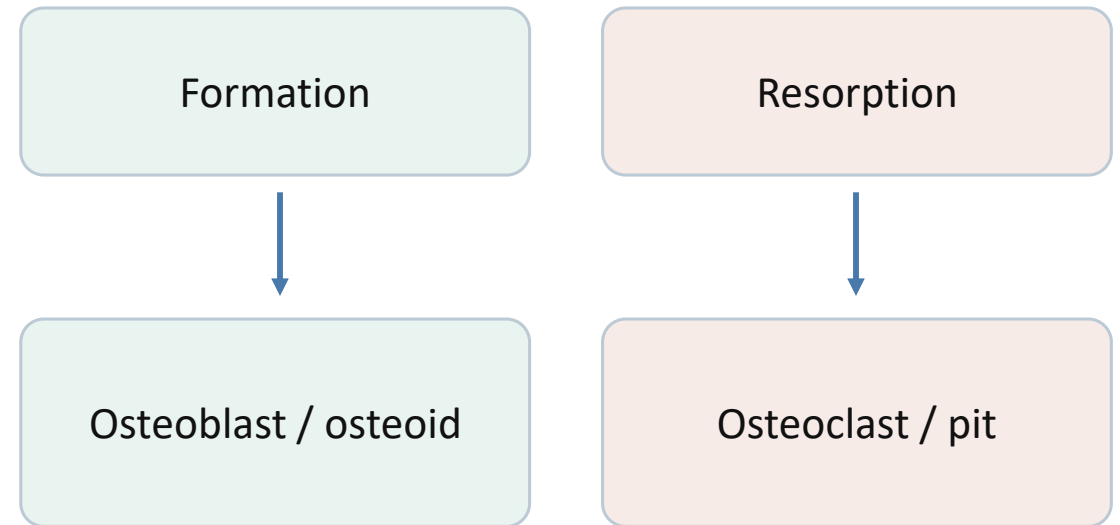


Schematic: Osteoclast over a sealed resorption site

Forming and resorbing cells are complementary

- Osteoblasts add matrix and control mineralization
- Osteoclasts remove mineral and organic matrix
- Coupling is needed to replace bone without net loss or excess

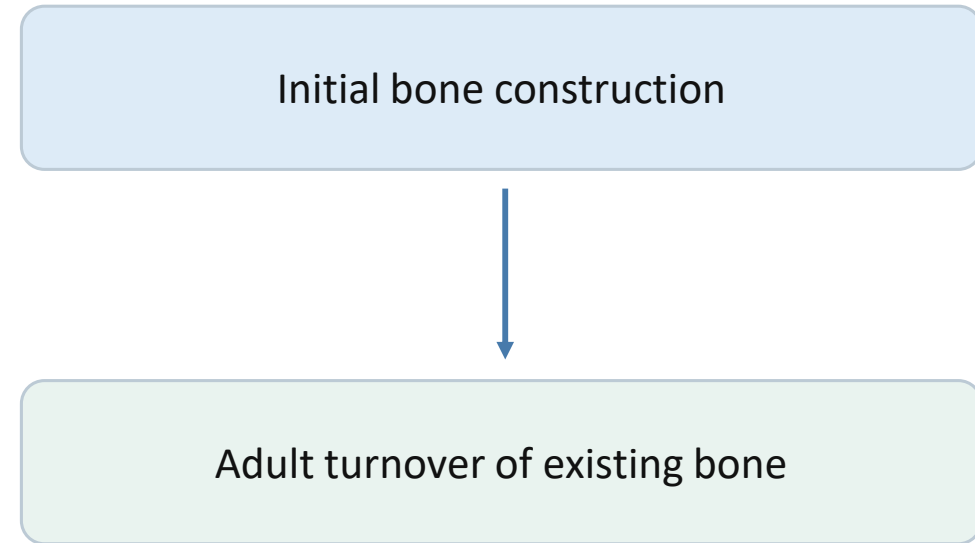
Schematic



Development is not identical to remodeling

Schematic

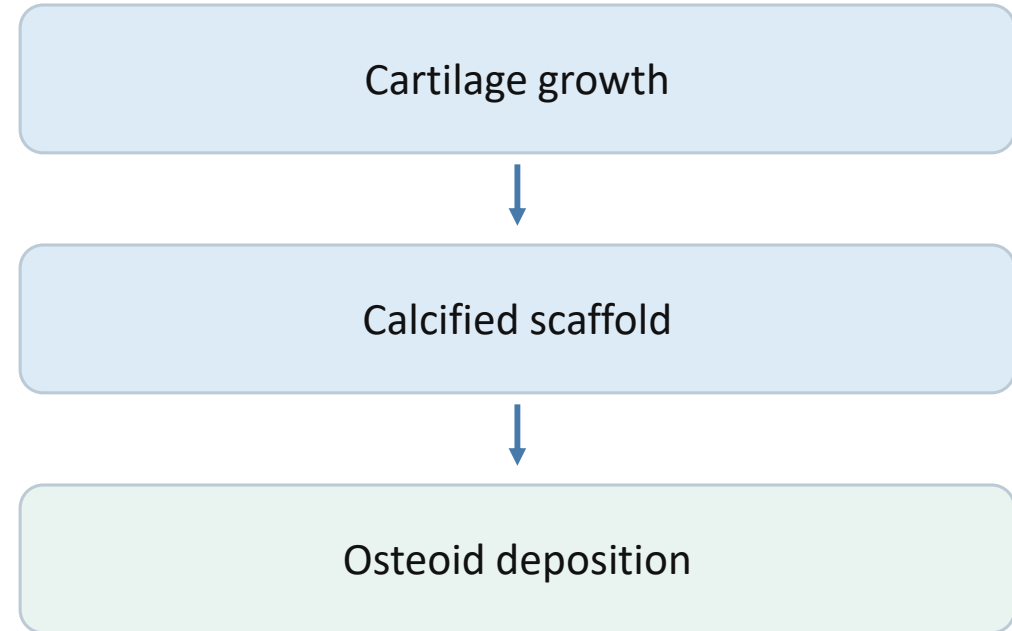
- Endochondral ossification builds bone on a cartilage template
- Intramembranous ossification forms bone directly in mesenchyme
- Adult remodeling renews bone that already exists



Endochondral formation establishes trabecular scaffolds

- Growth-plate cartilage proliferates and hypertrophies
- Cartilage matrix mineralizes and is invaded by vessels
- Osteoblasts deposit osteoid on residual cartilage struts

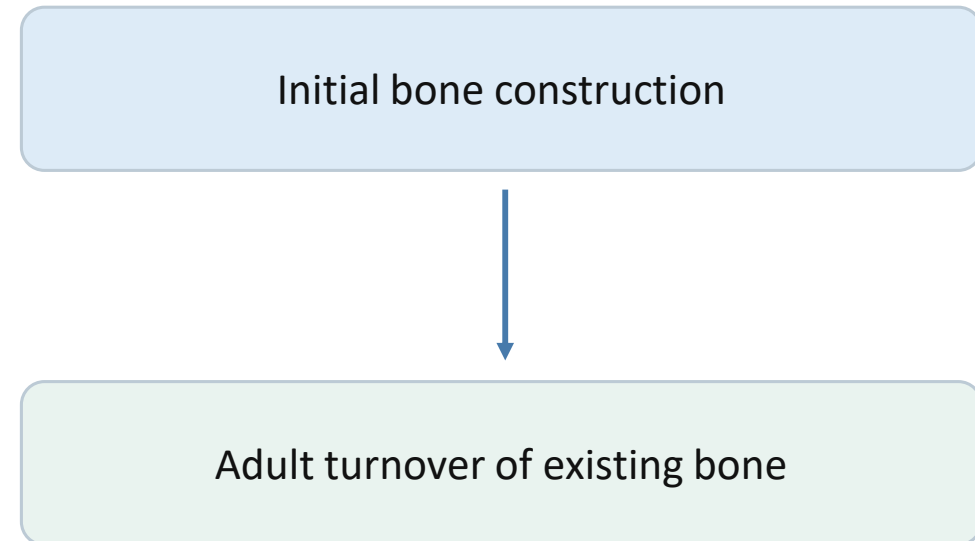
Schematic



Appositional growth differs from internal renewal

Schematic

- Flat bones may form by intramembranous ossification
- Osteoblasts add matrix to an existing surface during apposition
- Remodeling involves locally matched removal and replacement



Remodeling is continuous, not episodic growth

Schematic

- The adult skeleton is continuously reshaped by regulated turnover
- About 10% of the skeleton is turned over annually
- The rate is a broad textbook estimate, not a uniform site-specific rate

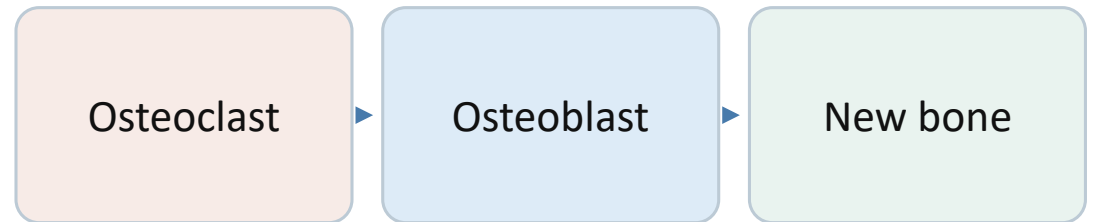


Approximate total skeletal turnover; Not site-specific

A basic multicellular unit coordinates turnover

- The BMU is a local unit of coupled cell activity
- Osteoclasts and osteoblasts operate sequentially at one surface
- Remodeling success depends on their coordinated actions

Schematic

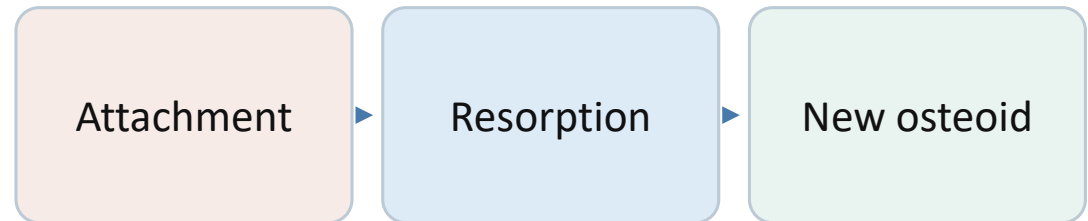


Schematic: Locally linked processes

The remodeling cycle has an ordered sequence

- Osteoclast attachment is followed by resorption
- Osteoblasts then attach and proliferate
- New matrix is synthesized at the remodeled surface

Schematic

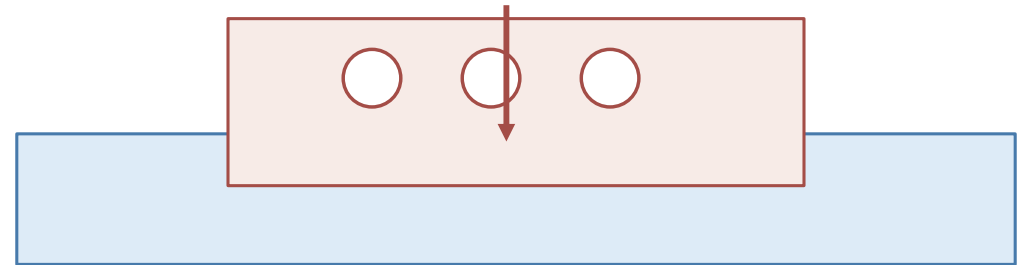


Schematic: Locally linked processes

The resorption phase removes existing material

- Osteoclasts occupy a defined bone-surface region
- Their resorption pit concentrates matrix dissolution
- The space generated becomes available for new deposition

Schematic

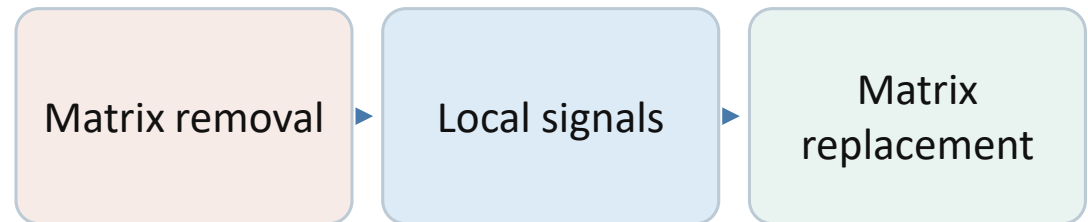


Schematic: Osteoclast over a sealed resorption site

Transition from removal to replacement is coupled

Schematic

- Removal of matrix is not the endpoint of remodeling
- Local cell–cell and soluble signals facilitate formation
- A coordinated handoff prevents persistent unreplaced defects

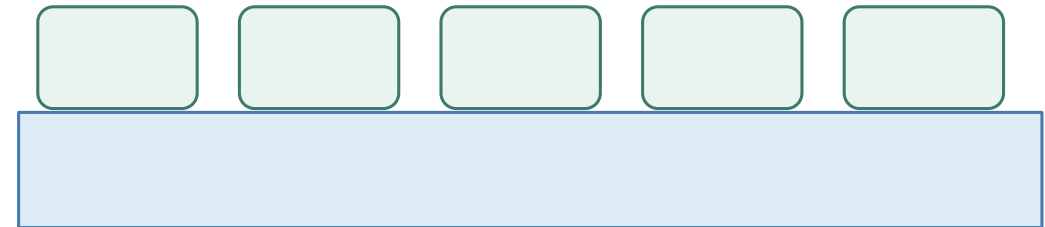


Schematic: Locally linked processes

Osteoblast recruitment precedes matrix synthesis

Schematic

- Osteoblast attachment and proliferation follow resorption
- Surface bone-forming cells replenish the remodeled site
- Matrix synthesis is the defining productive phase

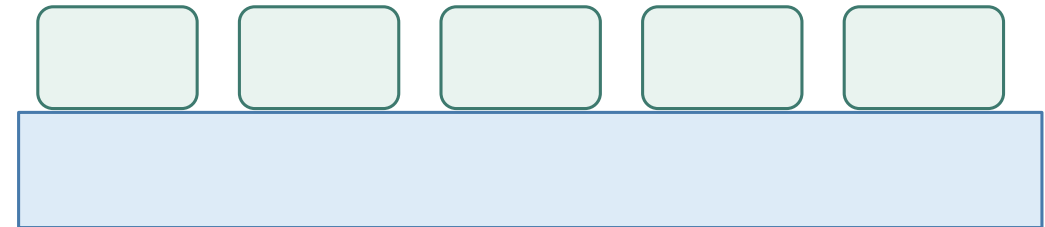


Schematic: Osteoblasts lining an osteoid surface

Mineralization consolidates newly formed osteoid

Schematic

- Osteoblasts regulate mineralization of the organic scaffold
- Mineral deposition adds hardness to the matrix
- Adequate matrix quantity and composition both matter

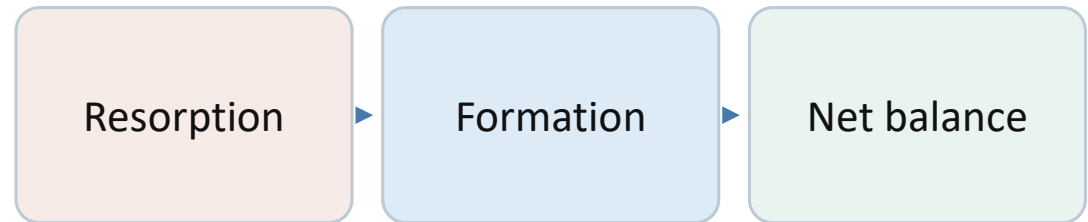


Schematic: Osteoblasts lining an osteoid surface

Remodeling is a balance, not a single reaction

- Resorption and formation are locally coupled
- The relative magnitudes of the two determine net balance
- Long-term imbalance changes skeletal mass

Schematic

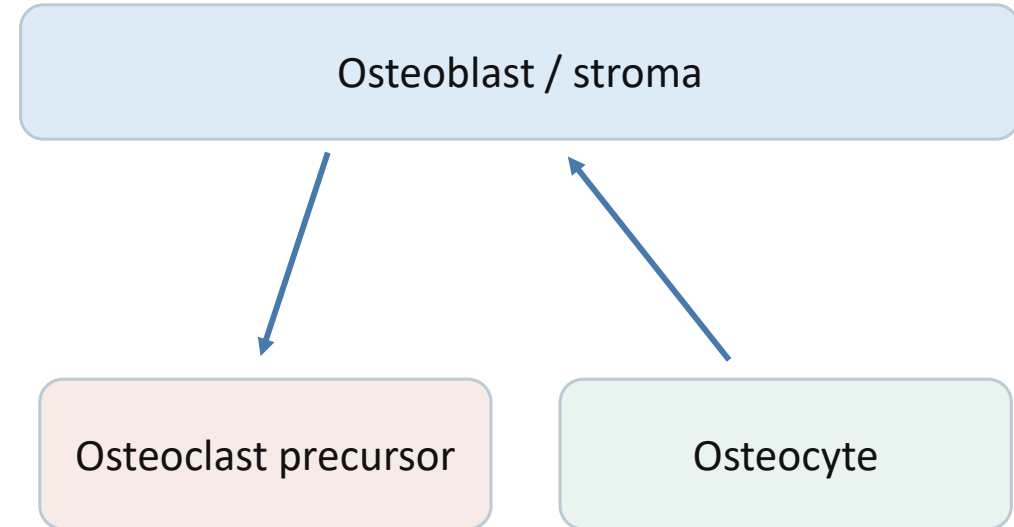


Schematic: Locally linked processes

Remodeling requires intercellular dialogue

- Osteoblasts and stromal cells instruct osteoclast precursors
- Osteocytes influence bone formation through sclerostin
- Resorbed matrix releases signals that can stimulate osteoblasts

Schematic

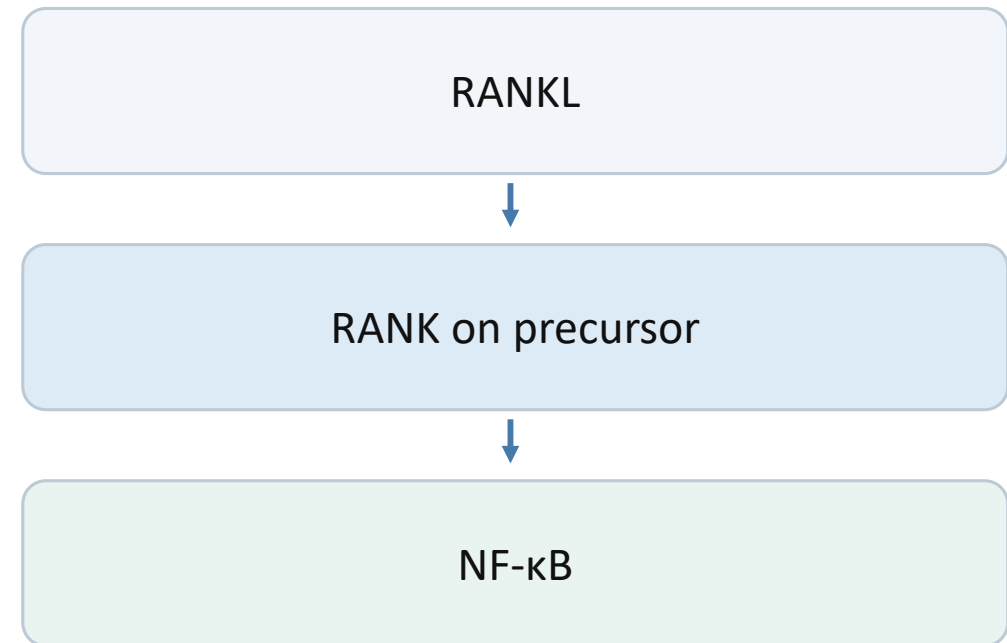


Schematic: Osteoblasts, precursors and osteocytes interact

RANK is displayed by osteoclast precursors

- RANK is a cell-surface receptor for RANK ligand
- Its activation promotes osteoclast generation and survival
- The downstream pathway prominently involves NF- κ B

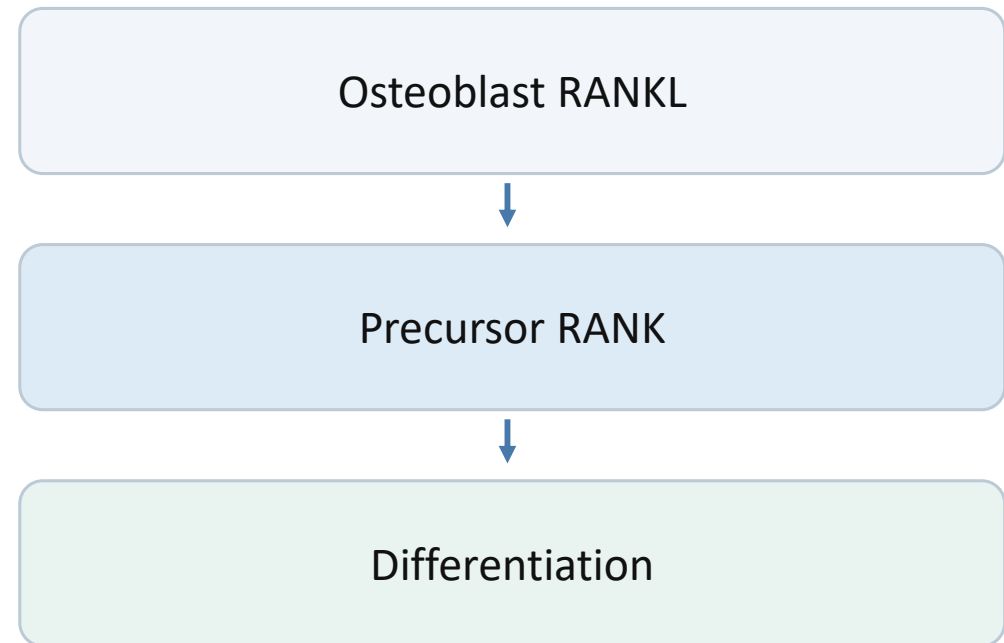
Schematic



RANKL supplies a differentiation signal

- RANKL is expressed by osteoblasts and marrow stromal cells
- Membrane-associated ligand binds RANK on precursors
- This contact initiates signaling toward osteoclast formation

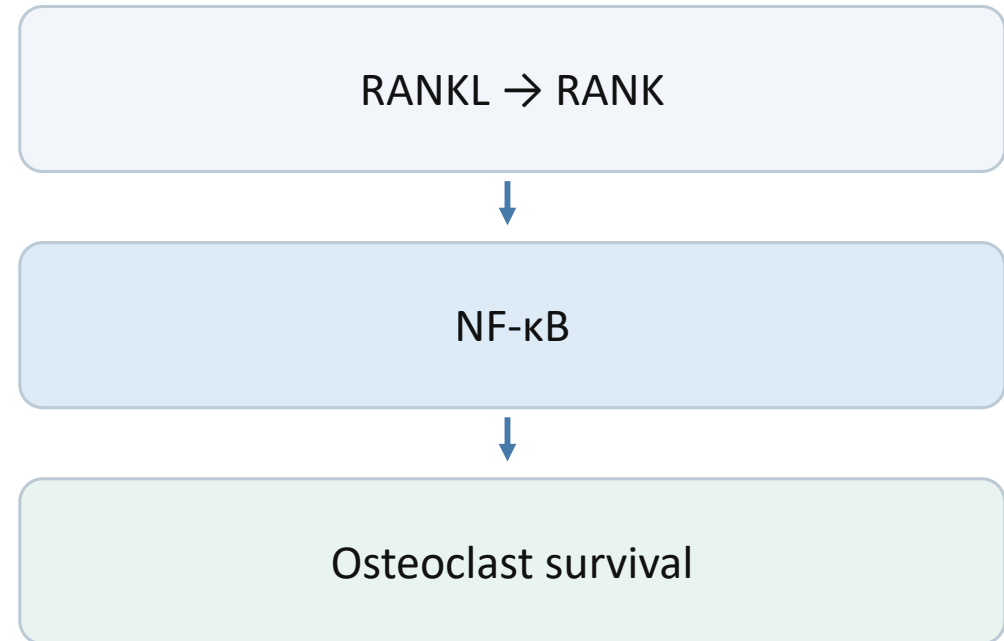
Schematic



RANK signaling activates NF-κB

- Engagement by RANKL activates signaling through RANK
- NF-κB is essential for osteoclast generation and survival
- Thus, stromal-cell signaling can control the resorptive arm

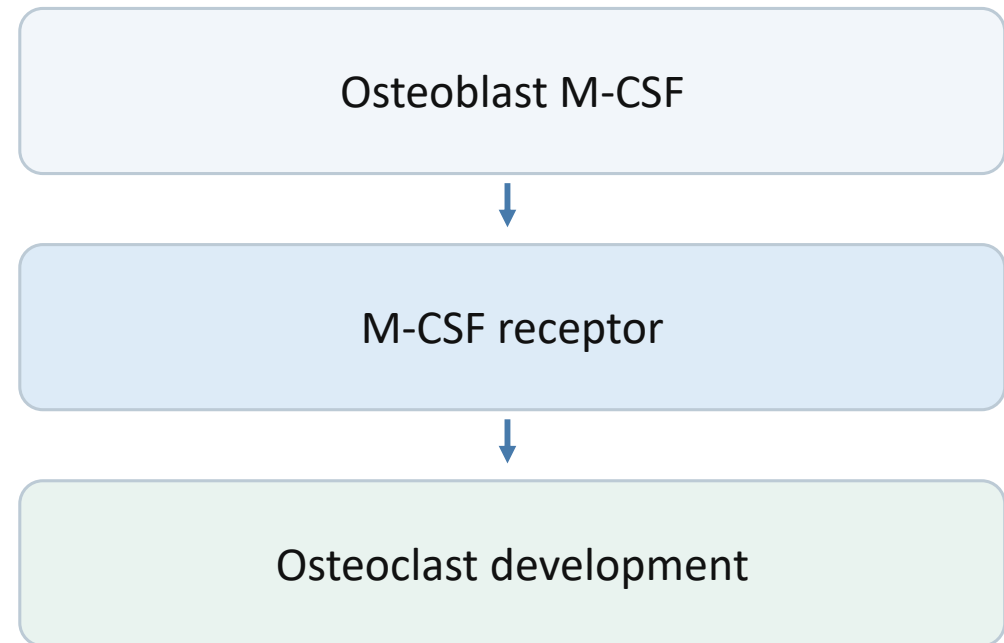
Schematic



M-CSF supplies another essential input

- Osteoblasts produce macrophage colony-stimulating factor
- The osteoclast precursor expresses an M-CSF receptor
- M-CSF is crucial for development of mature osteoclasts

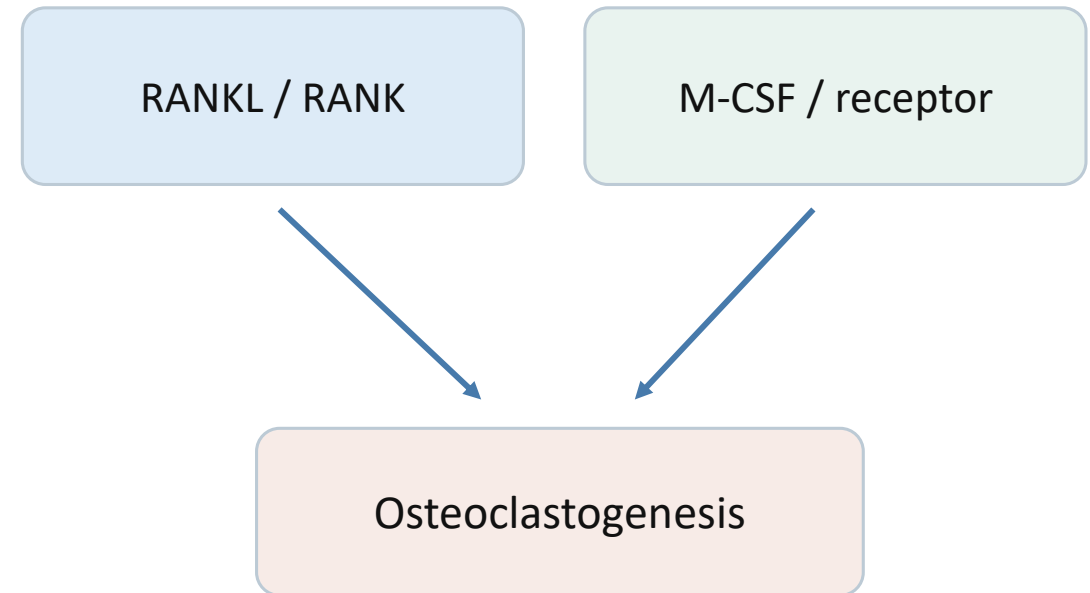
Schematic



RANKL and M-CSF cooperate in osteoclastogenesis

- Signals from osteoblast/stromal cells converge on precursors
- RANK/NF- κ B and M-CSF receptor signaling support differentiation
- The outcome is a functionally resorbing osteoclast

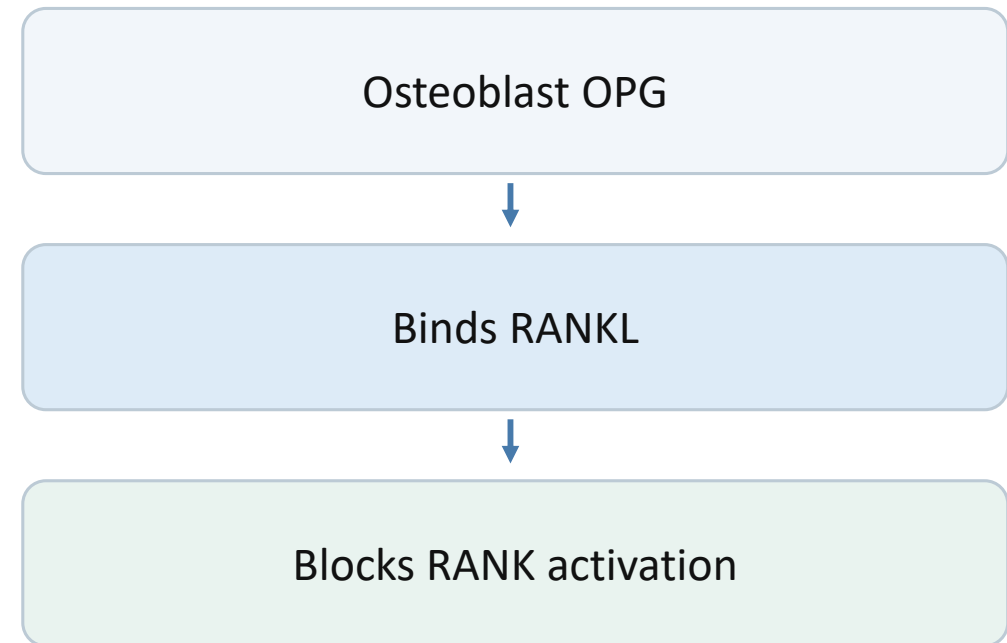
Schematic



OPG binds RANKL as a soluble decoy

- Osteoprotegerin (OPG) is secreted by osteoblasts and other cells
- It binds RANKL before the ligand reaches cellular RANK
- OPG therefore inhibits osteoclast differentiation

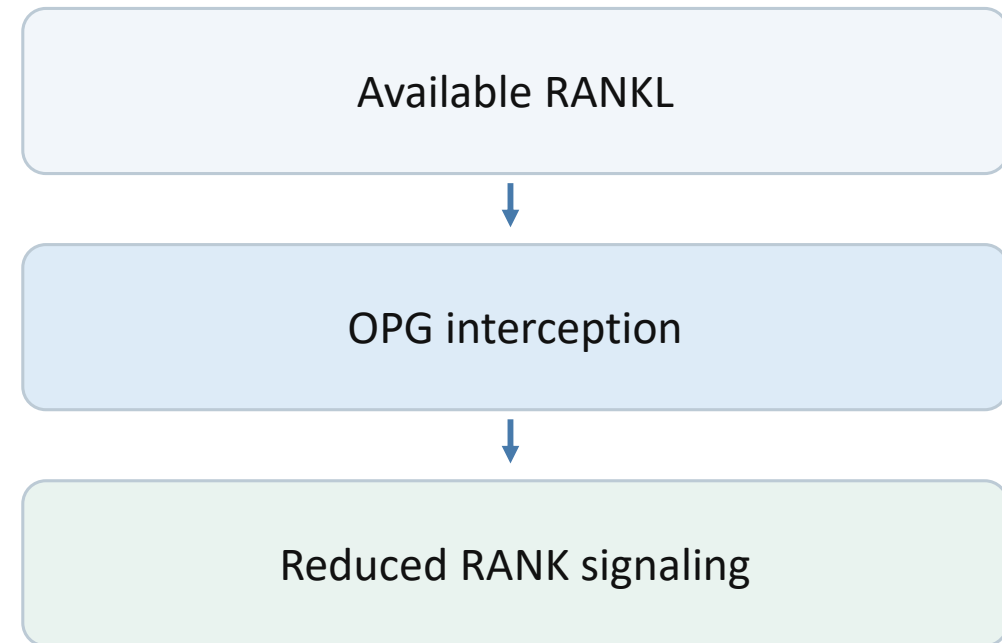
Schematic



OPG interrupts the ligand–receptor interaction

- RANKL normally links osteoblast/stromal cells to precursors
- OPG sequesters available RANKL
- Less signaling reaches RANK, reducing bone resorption

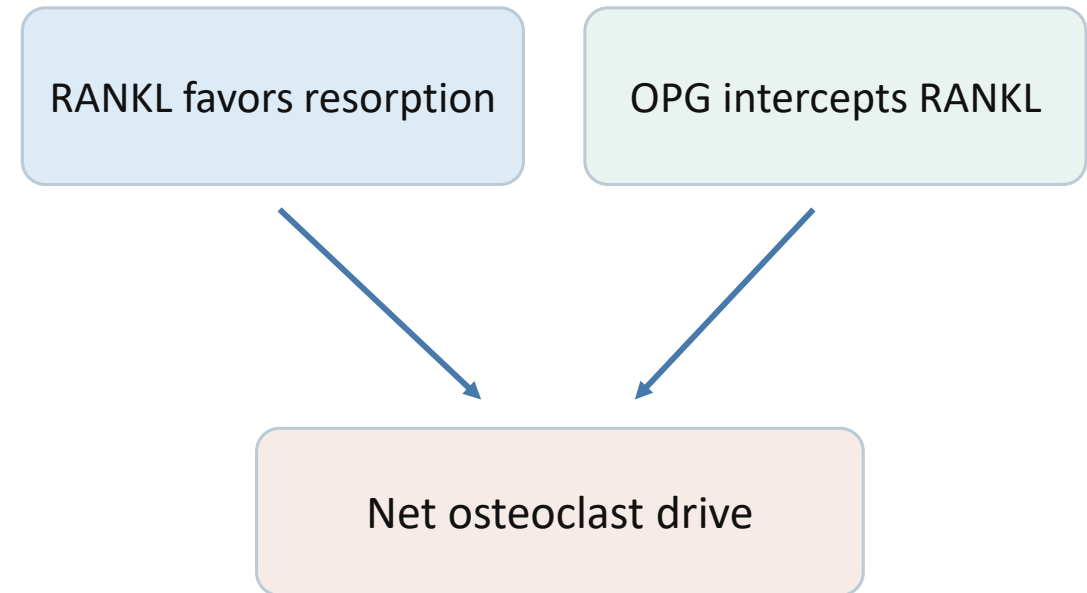
Schematic



RANKL availability relative to OPG matters

- High effective RANKL signaling favors osteoclast activity
- Higher OPG limits access of RANKL to RANK
- Changing this opposition shifts the resorption–formation balance

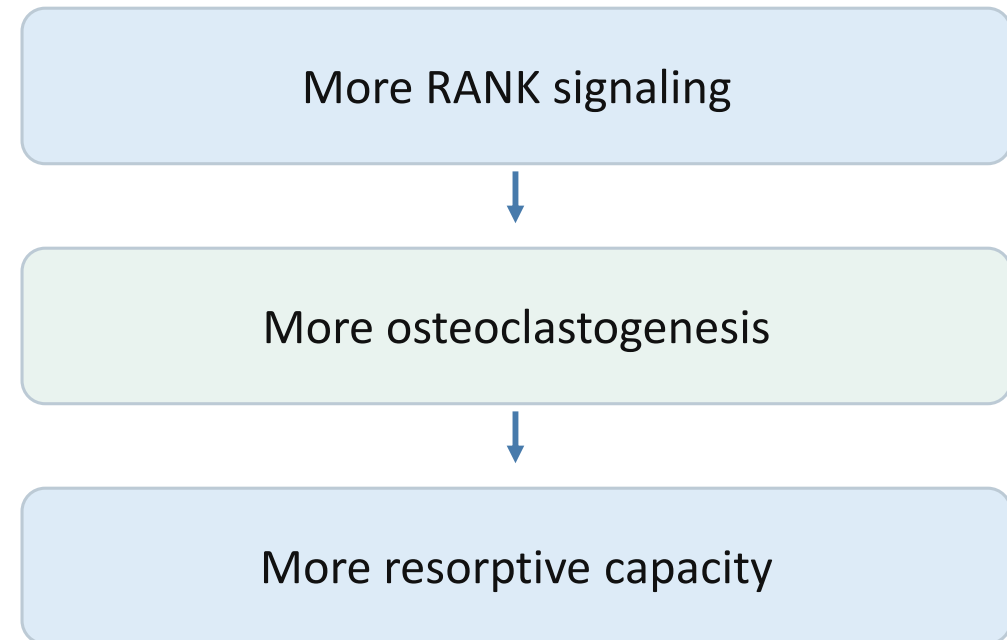
Schematic



Changes in signaling generate distinct outcomes

- Excessive osteoclast drive can favor net resorption
- Effective OPG inhibition favors relative protection from resorption
- The phenotype still depends on the coupled formation arm

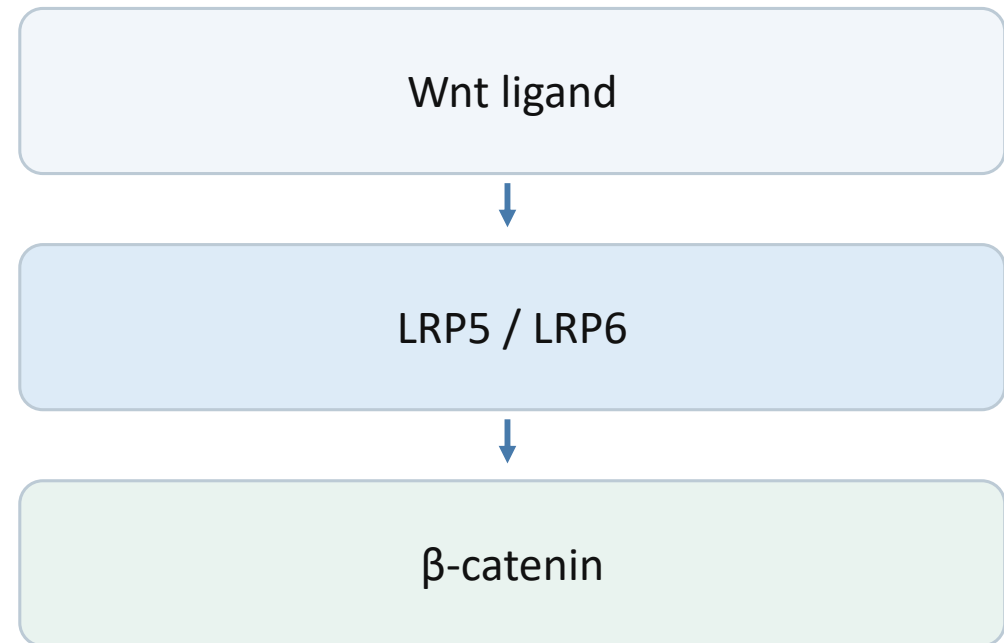
Schematic



Wnt links osteoprogenitors to osteoblasts

- Osteoprogenitor cells produce Wnt proteins
- Wnt binds the LRP5/LRP6 receptor system on osteoblasts
- This activates β -catenin-mediated signaling

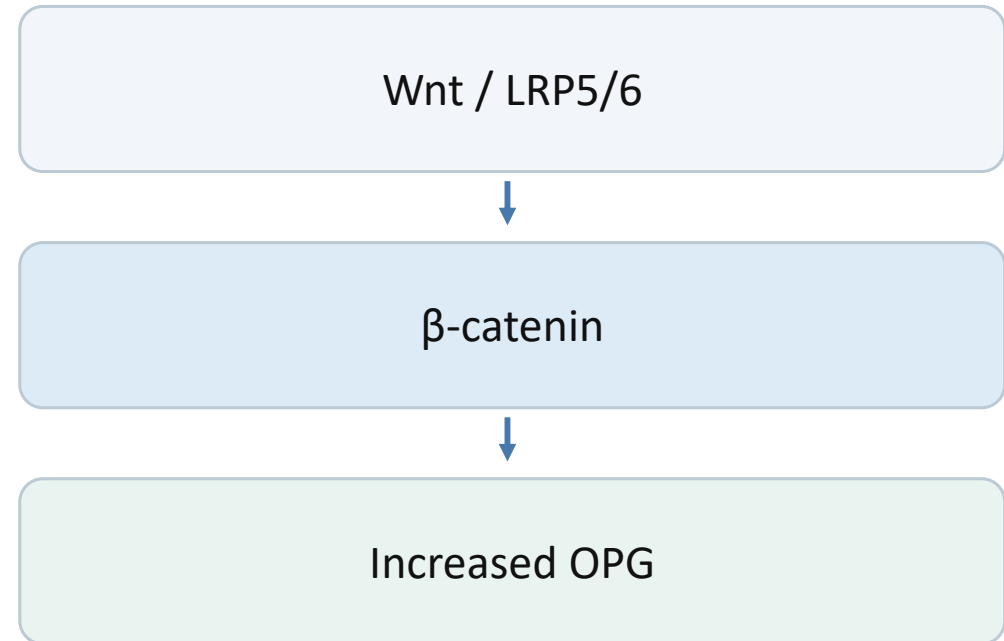
Schematic



β -catenin promotes the bone-forming program

- Wnt–LRP5/6 signaling activates β -catenin
- This pathway enhances the osteoblast-associated response
- It also promotes synthesis of OPG

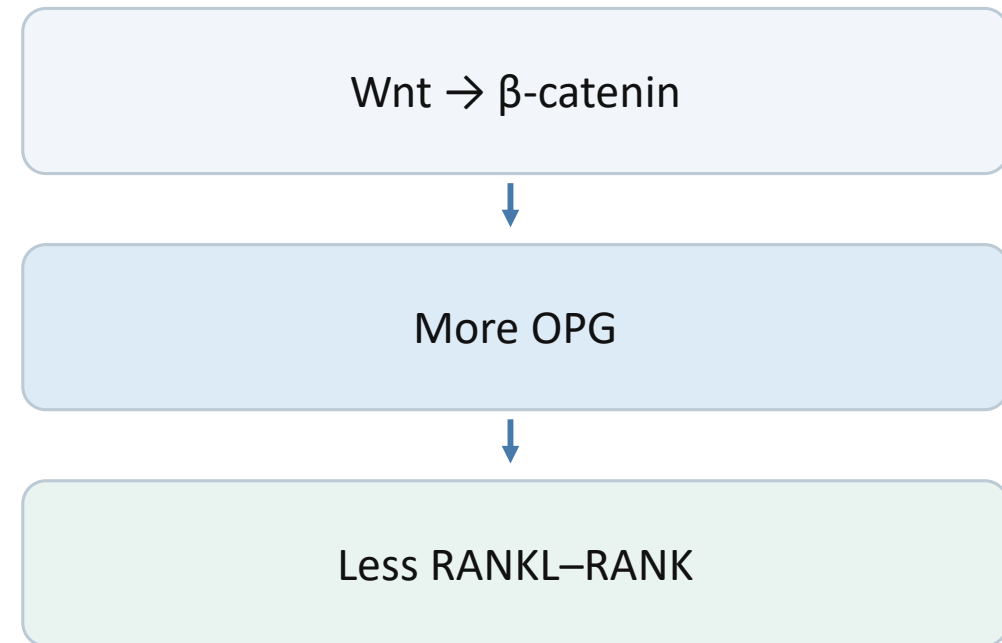
Schematic



Wnt indirectly restrains osteoclastogenesis

- Activation of Wnt signaling increases OPG synthesis
- OPG interferes with RANKL–RANK binding
- The resulting cross-talk suppresses osteoclast differentiation

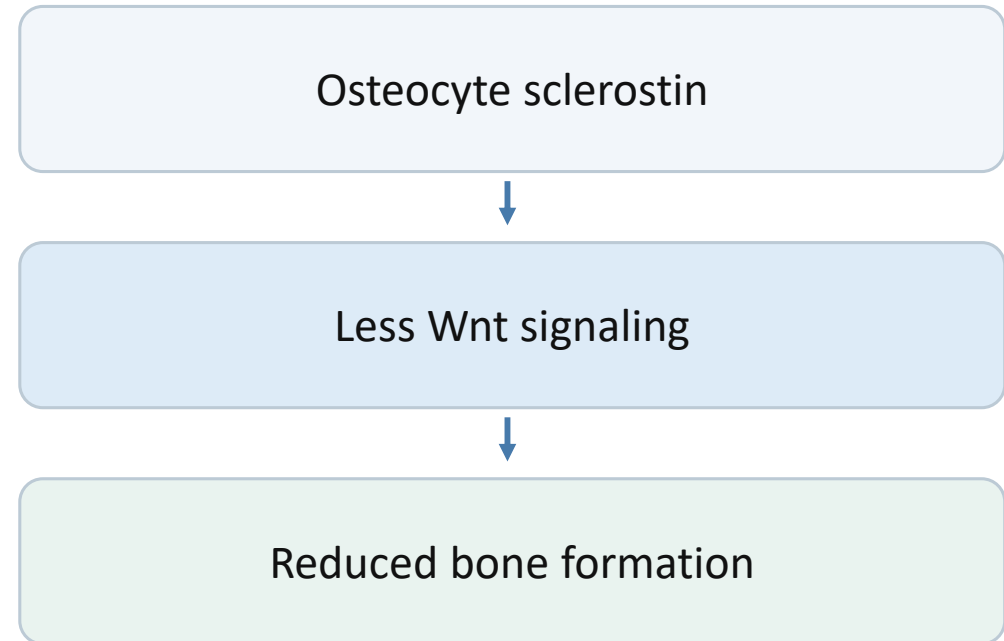
Schematic



Sclerostin is an osteocyte-derived inhibitor

- Osteocytes produce sclerostin
- Sclerostin inhibits Wnt/ β -catenin signaling
- The net consequence described is reduced bone formation

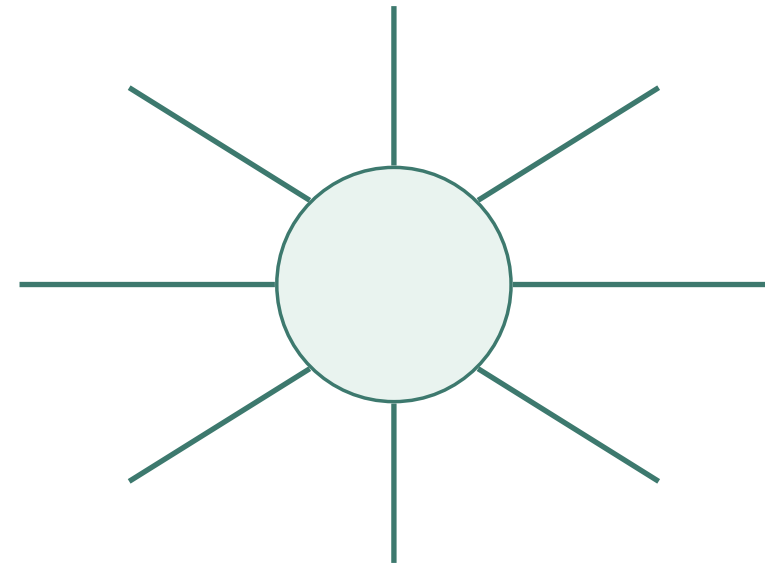
Schematic



Osteocytes can restrain osteoblast signaling

Schematic

- Osteocytes monitor mechanical force
- Their sclerostin signal antagonizes Wnt pathway activity
- The balance of these cues influences deposition of bone

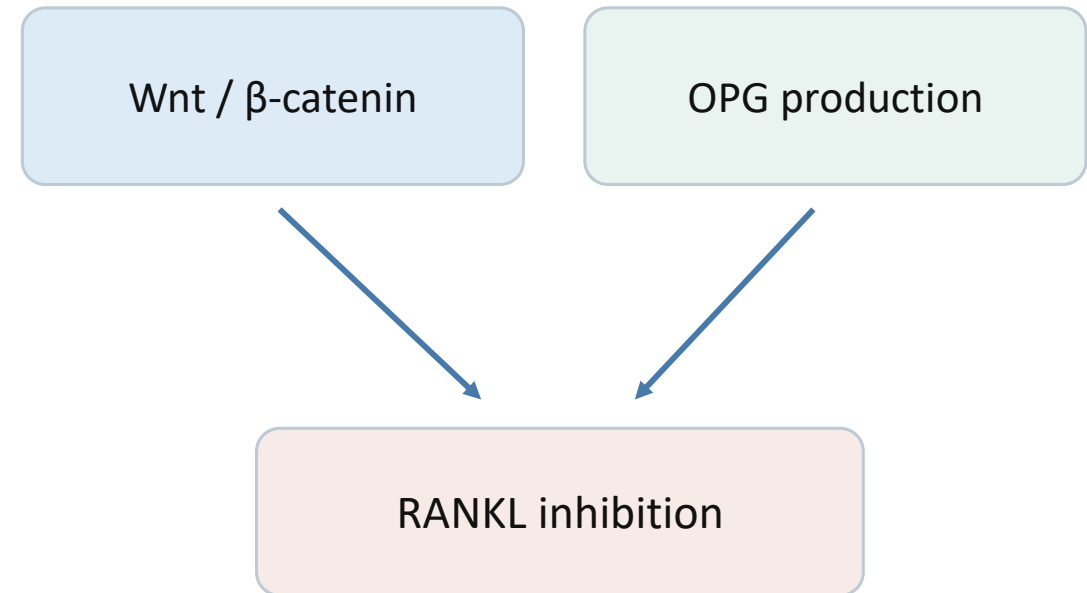


Schematic: Osteocyte mediates Wnt restraint

Wnt and RANK pathways intersect through OPG

- Wnt stimulates OPG production by bone-forming cells
- OPG neutralizes osteoclastogenic RANKL
- Formation-associated signaling thereby moderates resorption

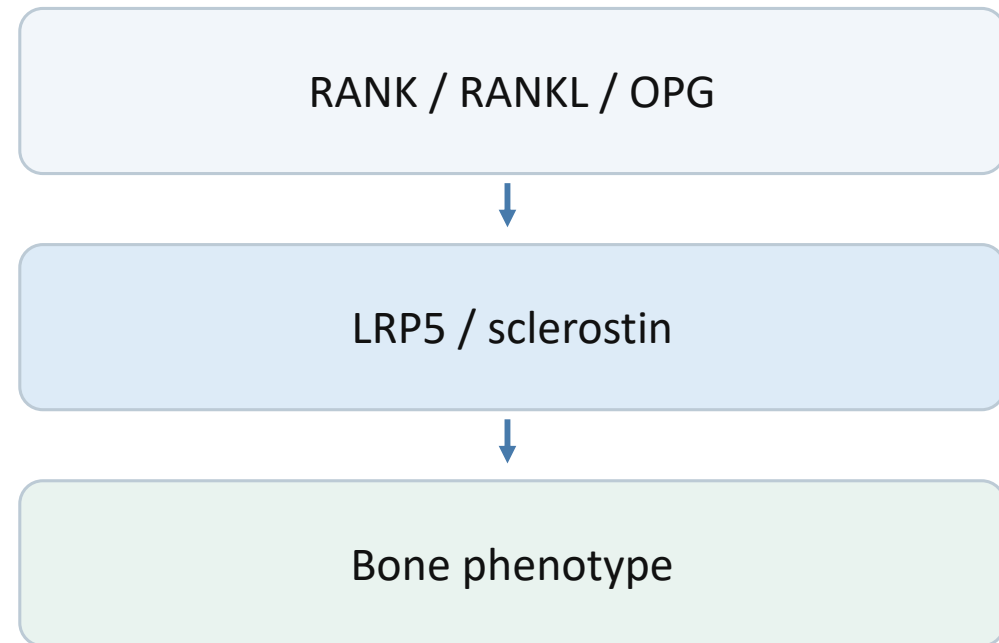
Schematic



Mutations establish pathway importance

- Rare germline defects affect RANK, RANKL and OPG
- Variants in LRP5 or sclerostin-related pathways also disturb bone
- Such alterations can cause severe congenital bone phenotypes

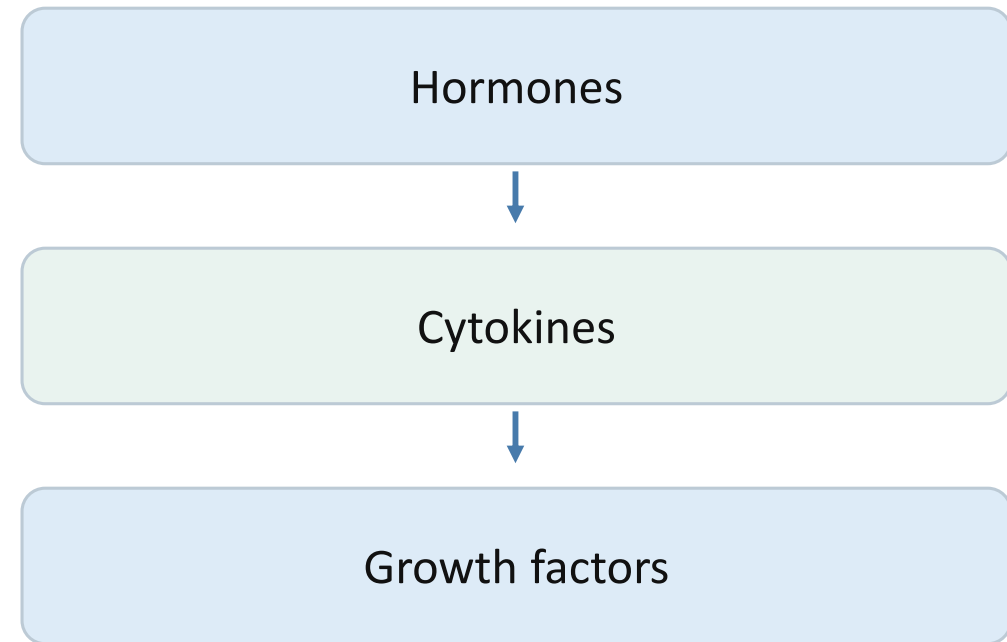
Schematic



Systemic hormones modify local cell signaling

- Parathyroid hormone, estrogen and testosterone influence turnover
- Glucocorticoids and vitamin D also modify remodeling
- Local cytokines and growth factors integrate these inputs

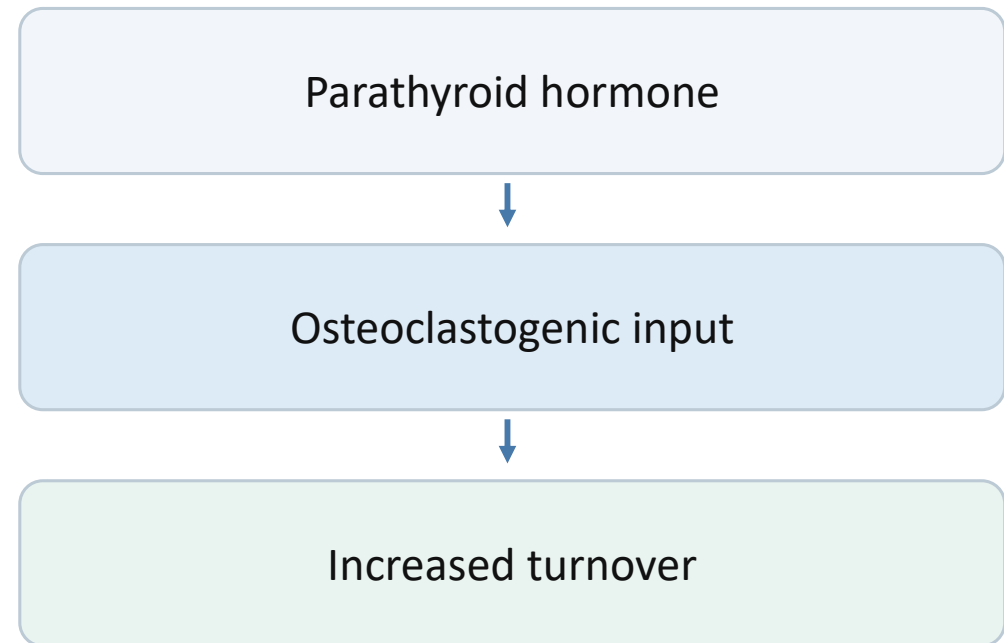
Schematic



PTH favors the resorptive arm in this context

- Parathyroid hormone influences cellular remodeling pathways
- Promotion of osteoclast differentiation
- Its effect is mediated within the osteoblast–osteoclast signaling network

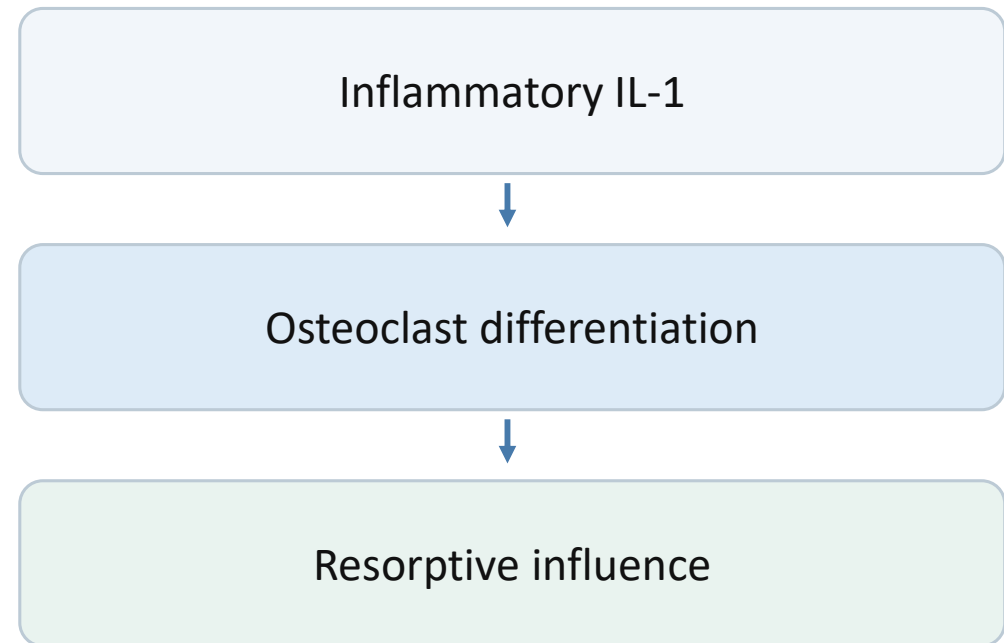
Schematic



IL-1 can promote osteoclast formation

- Interleukin-1 is an inflammatory cytokine
- The textbook associates IL-1 with increased osteoclast differentiation
- Inflammation can therefore alter local bone turnover

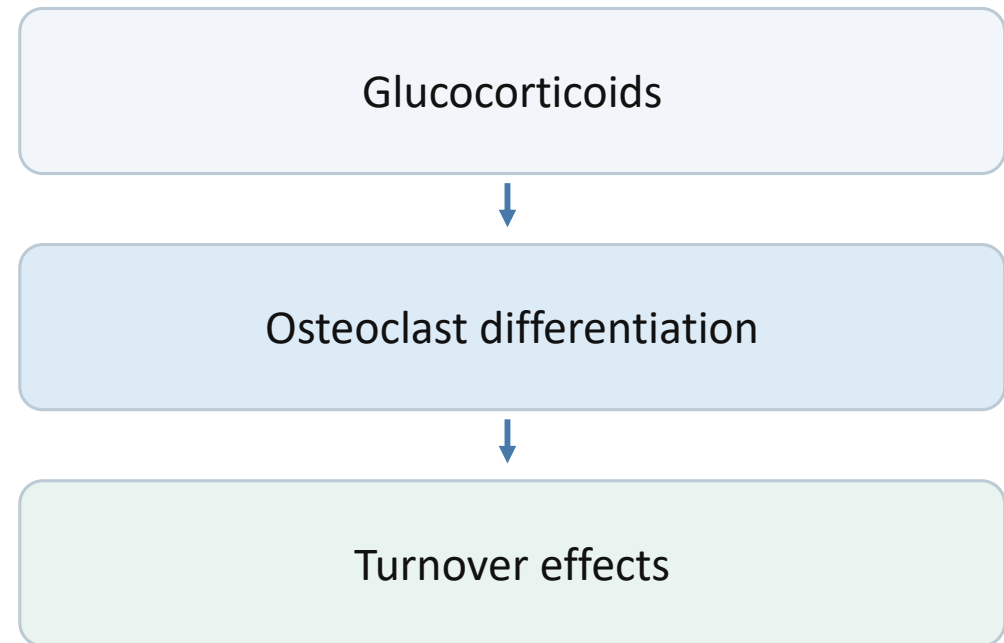
Schematic



Glucocorticoids shift remodeling signals

- Glucocorticoids are listed among systemic regulators
- In this source they promote osteoclast differentiation and turnover
- Their influence is embedded in RANK and Wnt pathway control

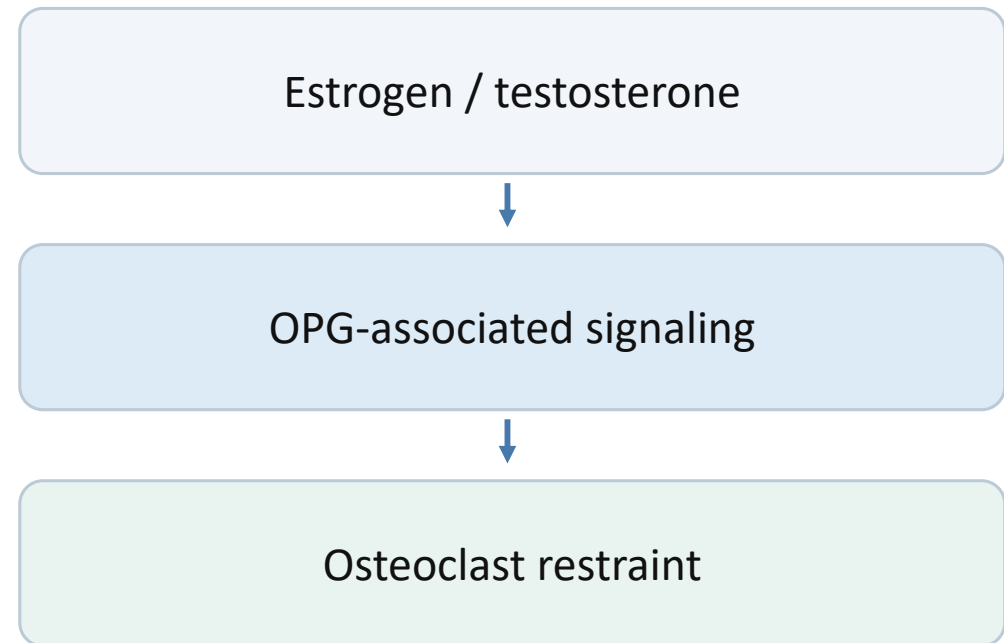
Schematic



Sex hormones favor OPG-associated restraint

- Estrogen and testosterone are systemic regulators of remodeling
- The source associates sex hormones with promotion of OPG
- An OPG-biased response limits osteoclast differentiation/activity

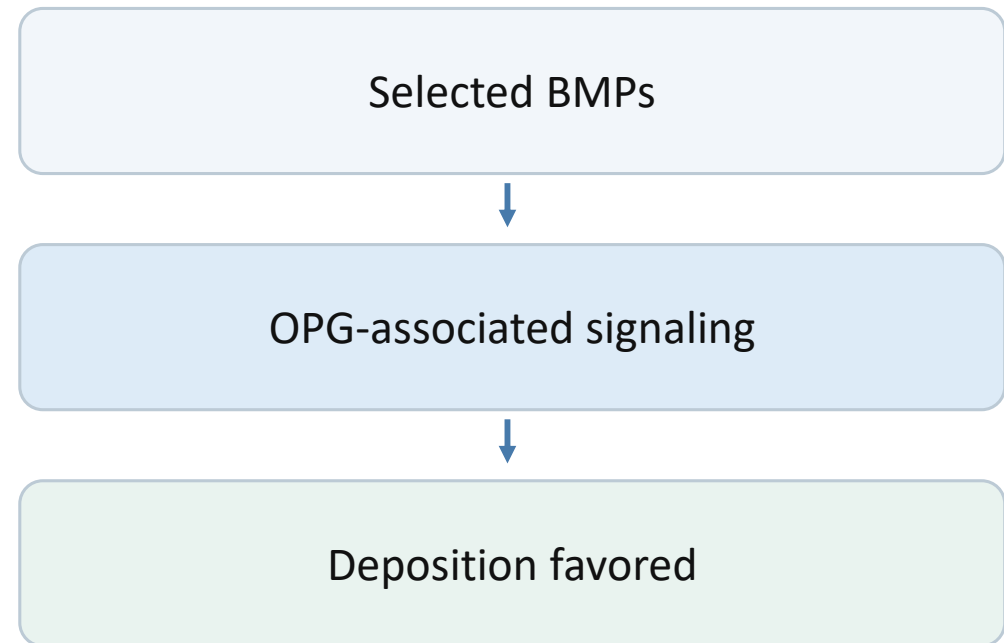
Schematic



BMPs also influence the resorption–formation balance

- Bone morphogenetic proteins are growth factors in bone biology
- Some BMPs can enhance OPG expression
- That shift favors deposition over excessive osteoclast activity

Schematic



Not all regulators have one fixed direction

- Vitamin D, cytokines and growth factors alter signaling balance
- A factor may act via multiple cellular components
- Interpret its effect through RANK/NF- κ B and Wnt/ β -catenin context

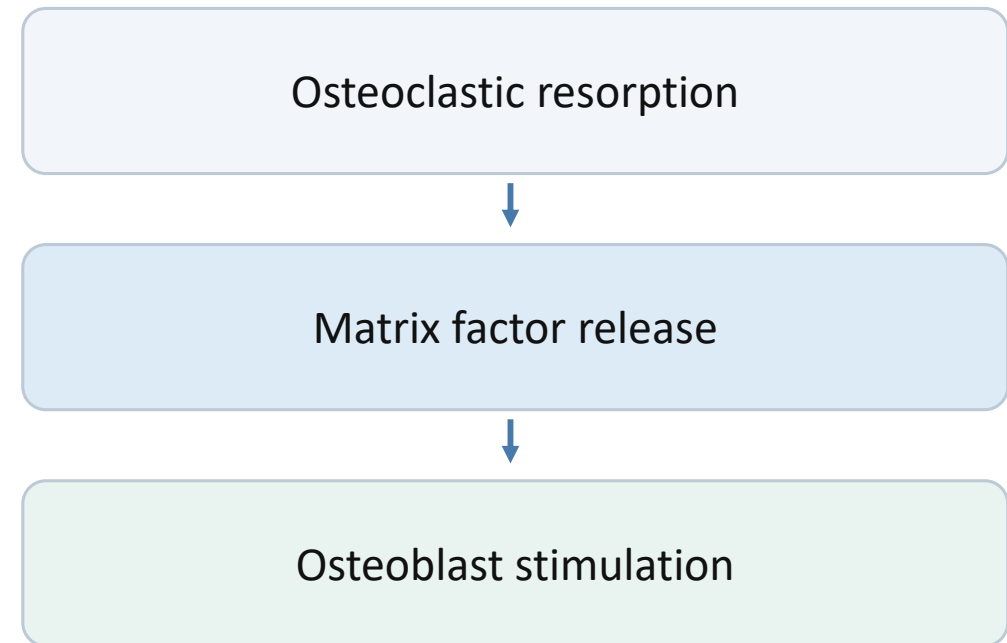
Schematic

Regulator	Source-described role
PTH, IL-1, glucocorticoids	Promote osteoclast differentiation
Some BMPs, sex hormones	Favor OPG-associated restraint
Vitamin D	Modulates remodeling pathways

Resorption releases matrix-sequestered signals

- Bone matrix stores growth factors and other soluble mediators
- Osteoclastic breakdown releases and activates some of them
- Some released factors subsequently stimulate osteoblasts

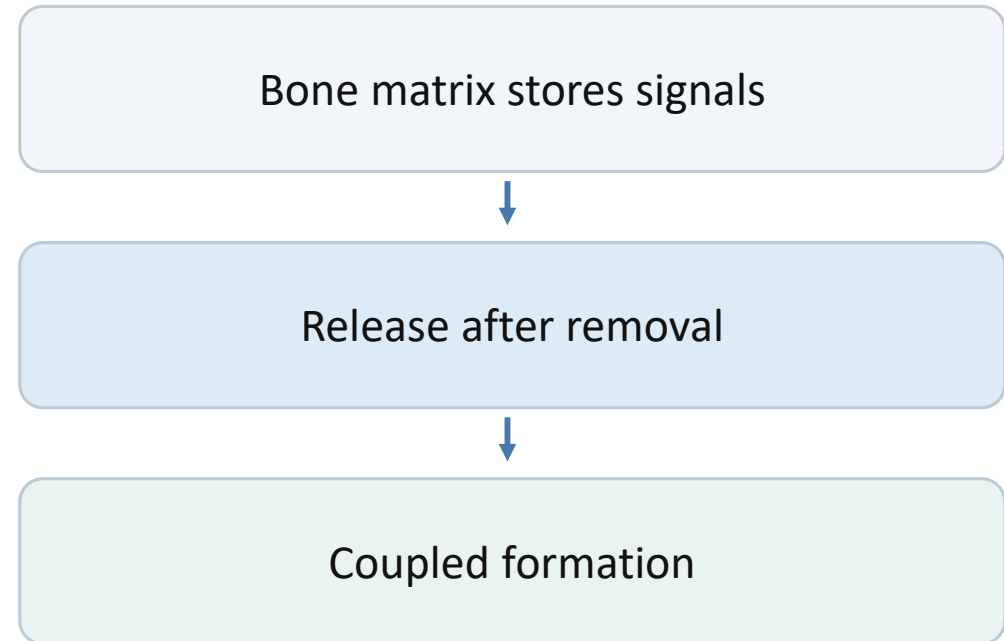
Schematic



The matrix is a reservoir for the next phase

Schematic

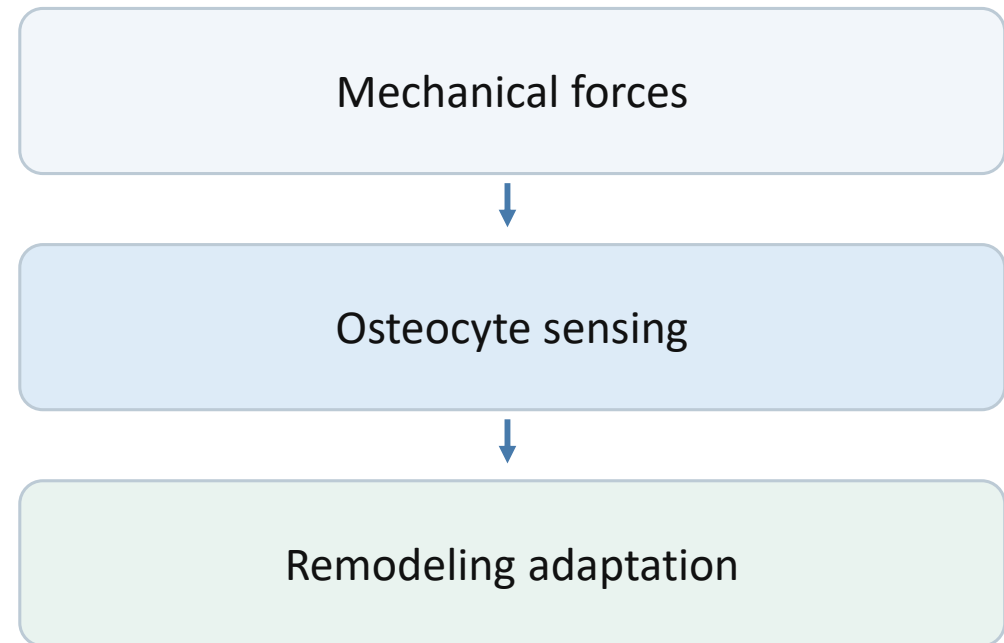
- Resorption dismantles existing bone
- Released signals alter the neighboring cellular microenvironment
- Local factors help initiate the formation phase



Mechanical forces can change remodeling geography

- Osteocytes detect the physical environment
- Cellular signals adjust remodeling in response to loading
- Consequent turnover can alter the shape of bones

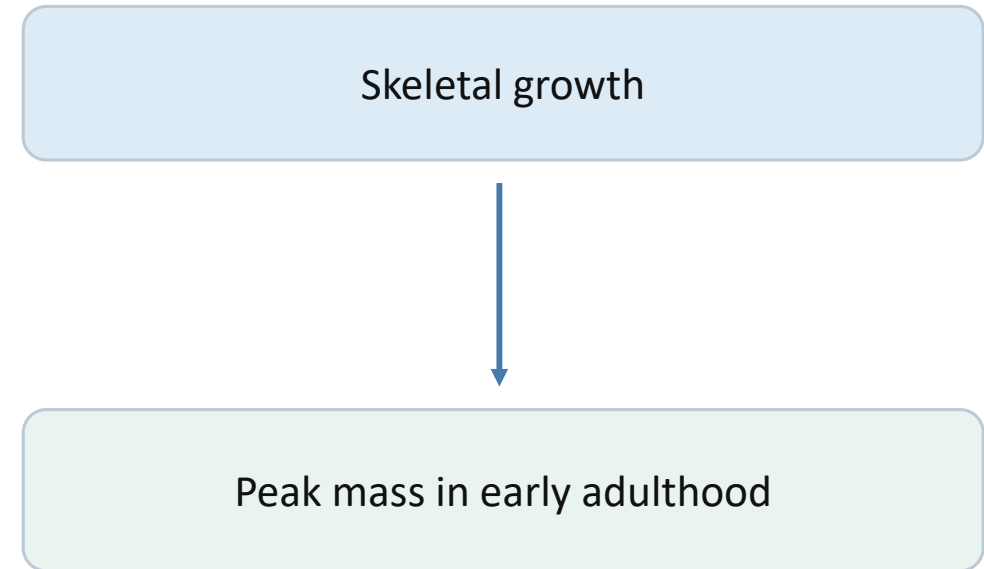
Schematic



Peak bone mass is reached in early adulthood

- Skeletal growth eventually ceases
- Peak bone mass follows cessation of skeletal growth
- Its magnitude affects the starting reserve for later age-related loss

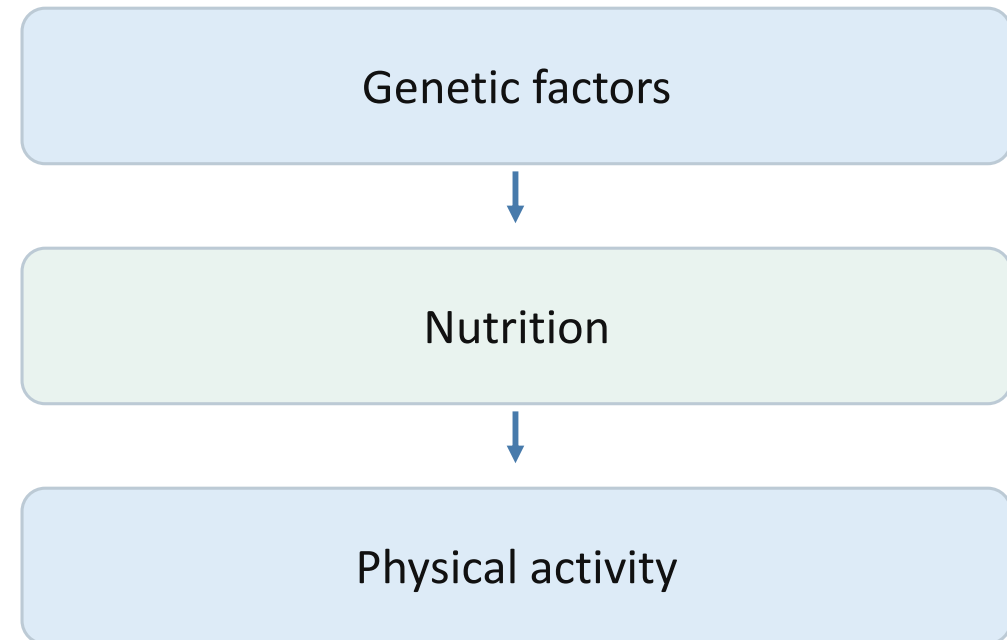
Schematic



Peak bone mass is multifactorial

- Genetic variation includes vitamin D receptor polymorphisms
- Nutrition contributes to the peak set point
- Physical activity is another important determinant

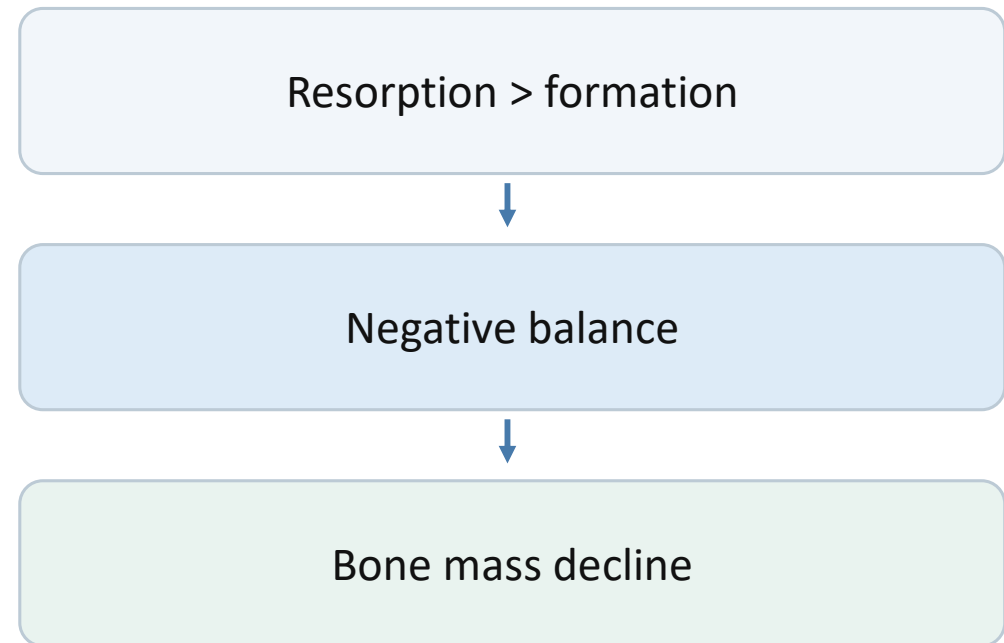
Schematic



Bone mass tends to decline from the fourth decade

- The source places onset of decline in the fourth decade
- At that stage, resorption progressively exceeds formation
- Persistent negative balance produces skeletal mass loss

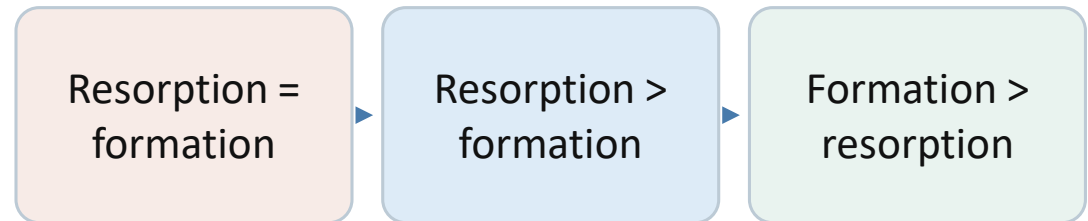
Schematic



Three balance states explain mass trajectories

Schematic

- Matched removal and deposition preserve bone mass
- Relative excess resorption creates negative balance
- Relative excess deposition creates positive balance

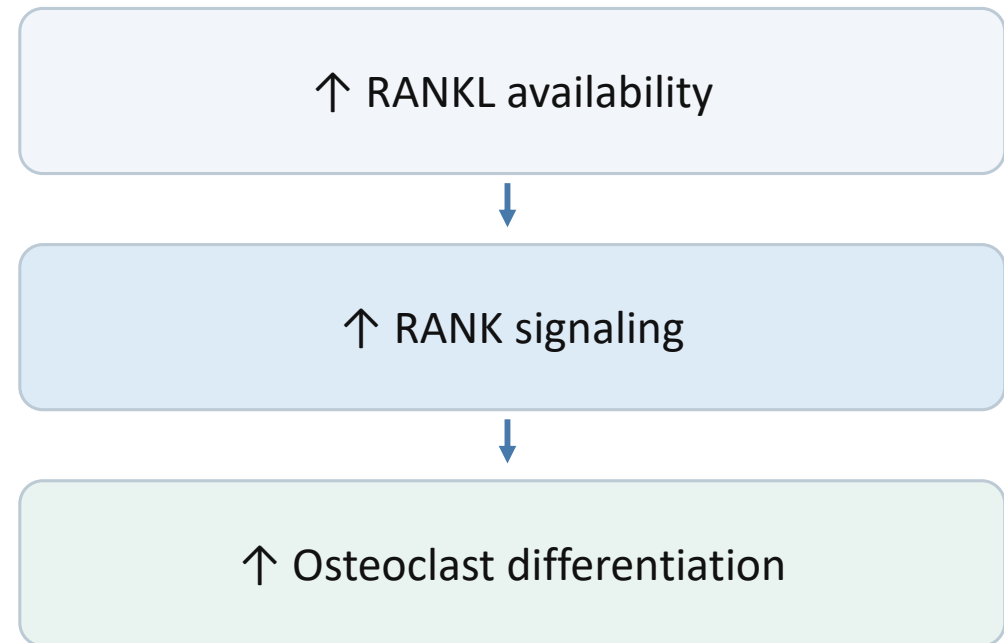


Schematic: Locally linked processes

Case: Stronger RANKL drive

Schematic

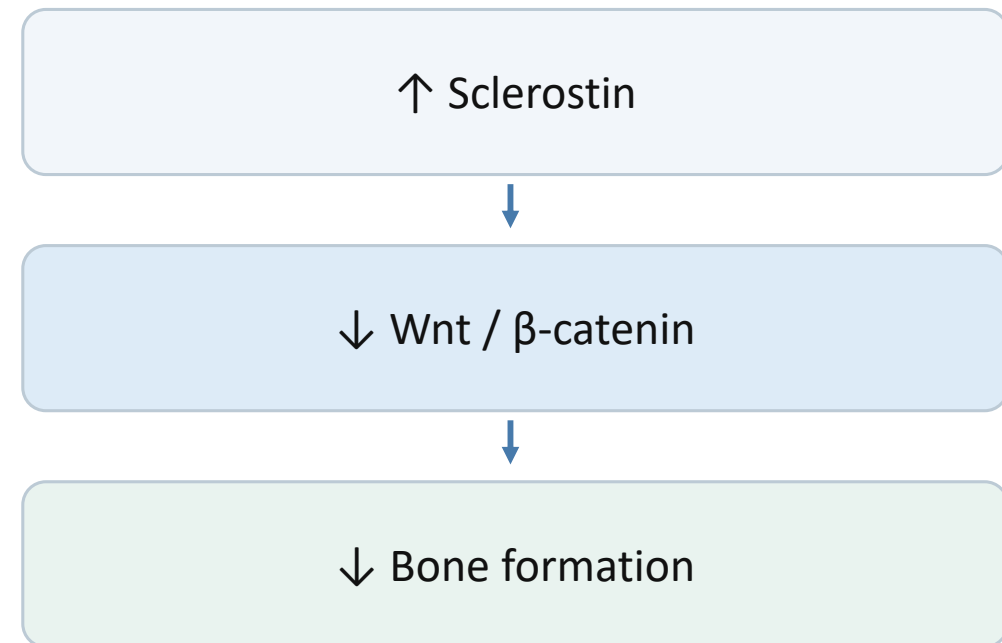
- Hypothetical: RANKL availability increases while OPG is unchanged
- Predict the immediate cellular response
- Explain the most likely direction of resorption



Case: Enhanced sclerostin signaling

Schematic

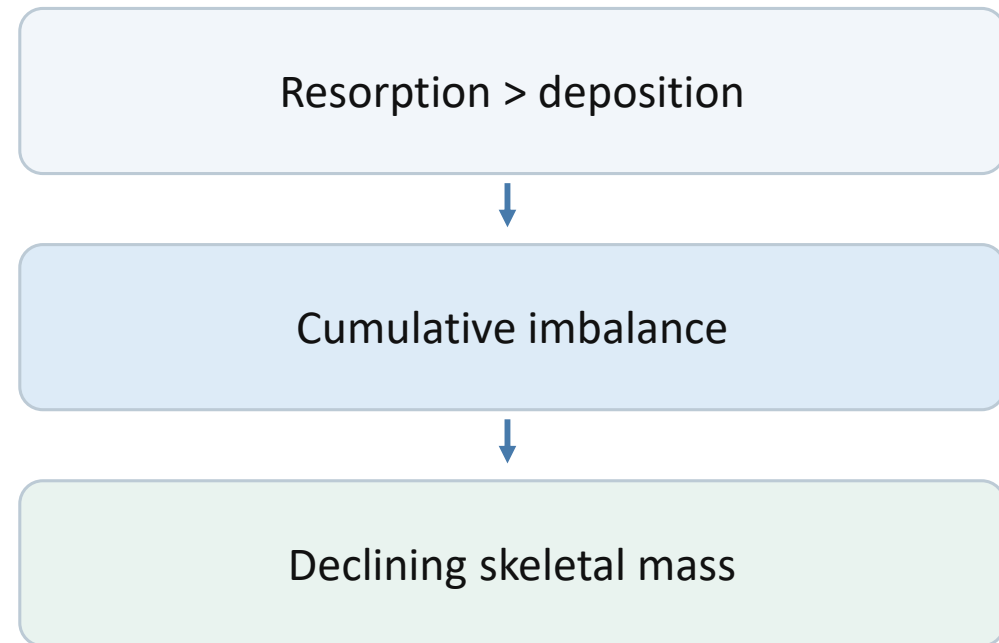
- Hypothetical: Osteocyte sclerostin signaling increases
- Predict the Wnt/ β -catenin effect
- Identify the direct consequence for bone formation



Case: Turnover becomes uncoupled with age

Schematic

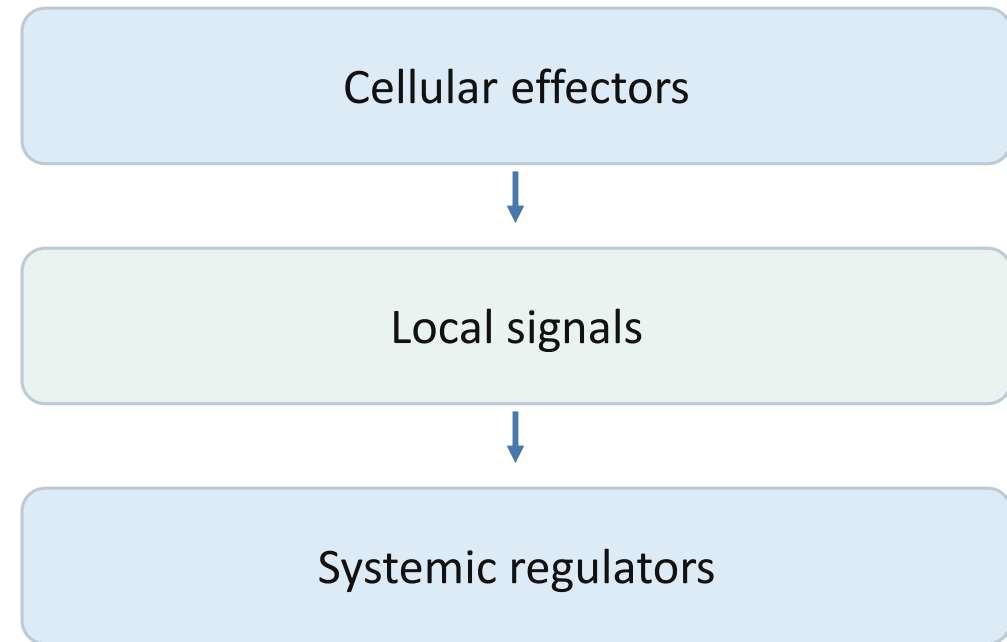
- Hypothetical: Bone resorption persistently exceeds formation
- State the expected long-term mass trend
- Connect the mechanism to the source-described fourth-decade pattern



Cellular, local, and systemic levels interact

Schematic

- Osteoblasts and osteoclasts execute the BMU sequence
- RANK, OPG, M-CSF and Wnt determine local differentiation signals
- Hormones, cytokines and mechanical force modify the outcome



Summary: Remodeling maintains skeletal integrity

- Continuous turnover renews damaged matrix
- RANKL–RANK and M-CSF favor osteoclast development
- OPG and Wnt oppose excess resorption; Sclerostin restrains formation
- Long-term imbalance changes bone mass

Schematic

Resorption	RANKL / RANK; M-CSF
Restraint of resorption	OPG
Osteoblast / OPG signaling	Wnt / β -catenin
Formation restraint	Sclerostin

Integrated prediction: increased Wnt signaling

- Hypothetical: Wnt/ β -catenin signaling is enhanced in osteoblasts
- Predict the direction of OPG synthesis
- Infer the resulting change in RANKL-dependent osteoclast formation
- Separate the primary osteoblast signal from the secondary effect on resorption

Schematic

