Mechanisms of Bone Remodeling

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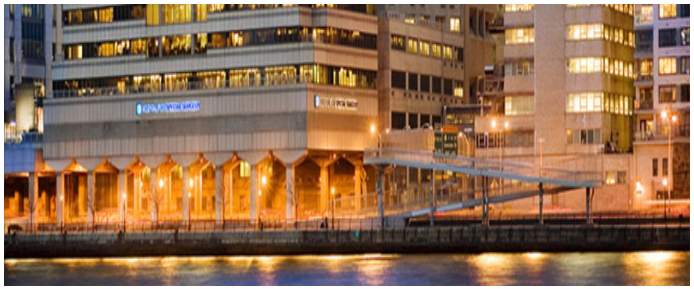
New York, NY

Disclosures

- *Consultant: Fidia, Bone Therapeutics, Jannsen Pharmaceutical, Novartis, Roche*
- *Research Grant: Boehringer Ingelheim*



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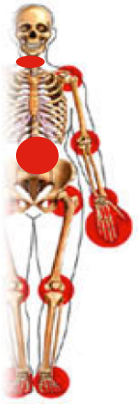
Outline

- **General principles of physiological bone remodeling**
- **Mechanisms of physiological “coupling” of bone resorption and formation**
- **Mechanism of de-regulated bone remodeling in inflammatory arthritis (RA and SpA)**

Cellular mechanisms of physiological bone adaptation

- **Any alterations in the structure, composition and/or properties of skeletal tissues in the post-natal period are dependent on these biologic and cellular processes:**

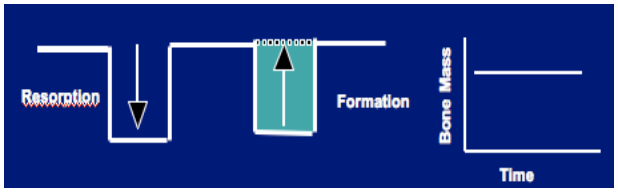
  - **Remodeling:** resorption/formation
    - *osteoclasts/osteoblasts*
  - **Modeling:** formation
    - *osteoblasts*
  - **Endochondral:** formation
    - *chondrocyte/osteoclast/osteoblast*



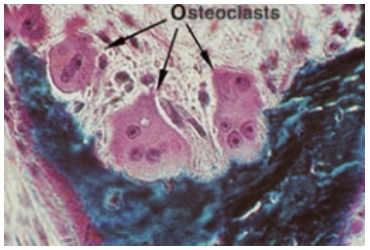
These same cellular processes mediate the skeletal changes in *inflammatory and rheumatic diseases*-**but,** the activities of the cells are de-regulated resulting in pathological alterations in the structural and functional properties of bone (locally and potentially systemically).

Physiologic Bone Remodeling

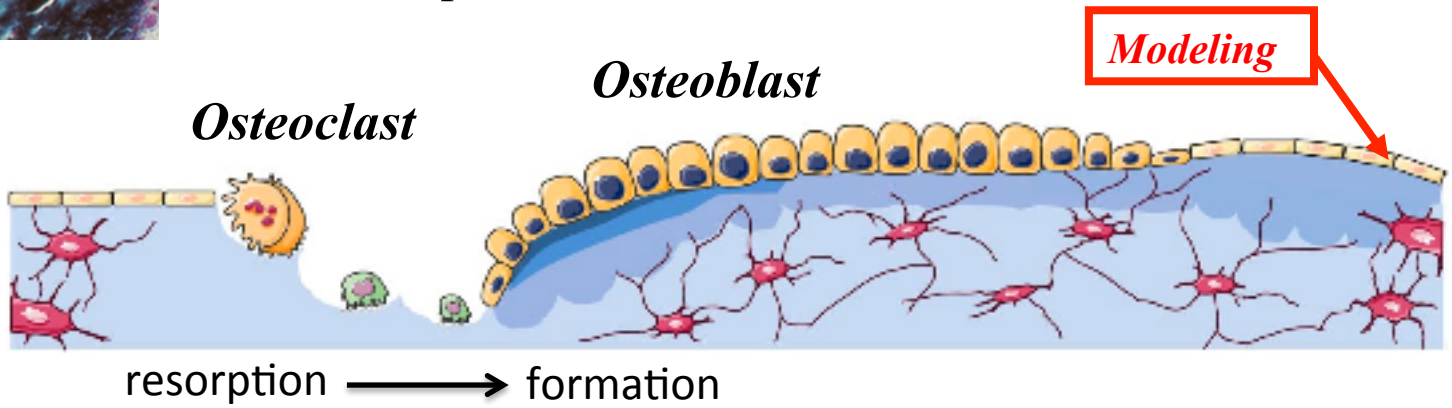
- Adapt shape and structural organization to alterations in biomechanical forces
- Maintain structural integrity
  - Repair microdamage
- Maintain mineral ion homeostasis



Resorption=Formation
"Coupled"



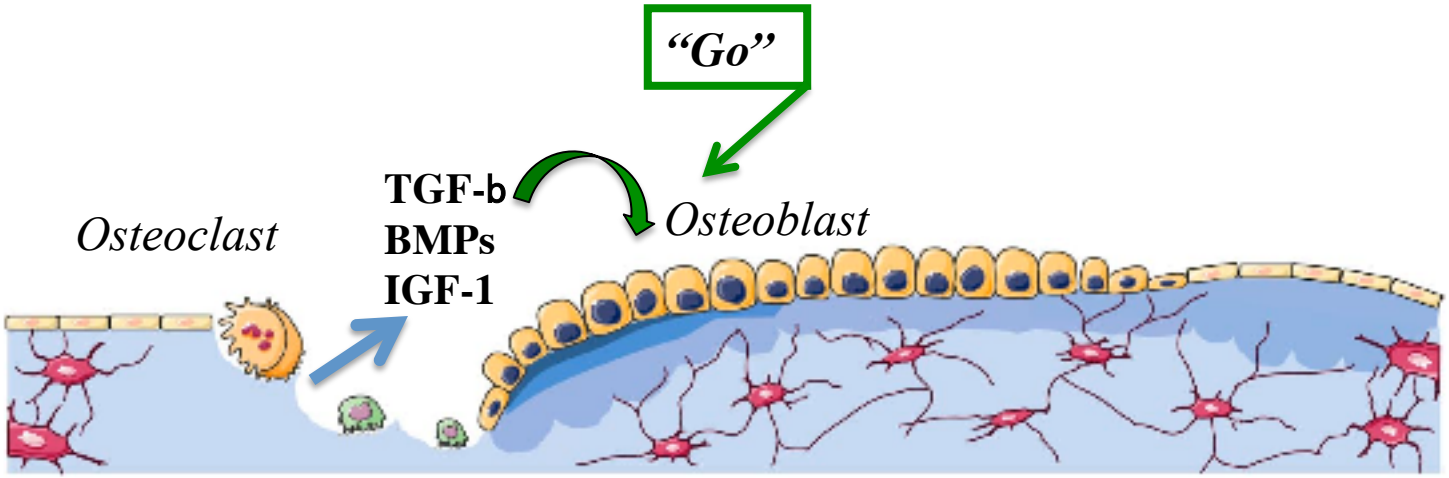
Osteoclasts are required for bone resorption



Question: What are the mechanisms of *coupling* of bone resorption/formation?

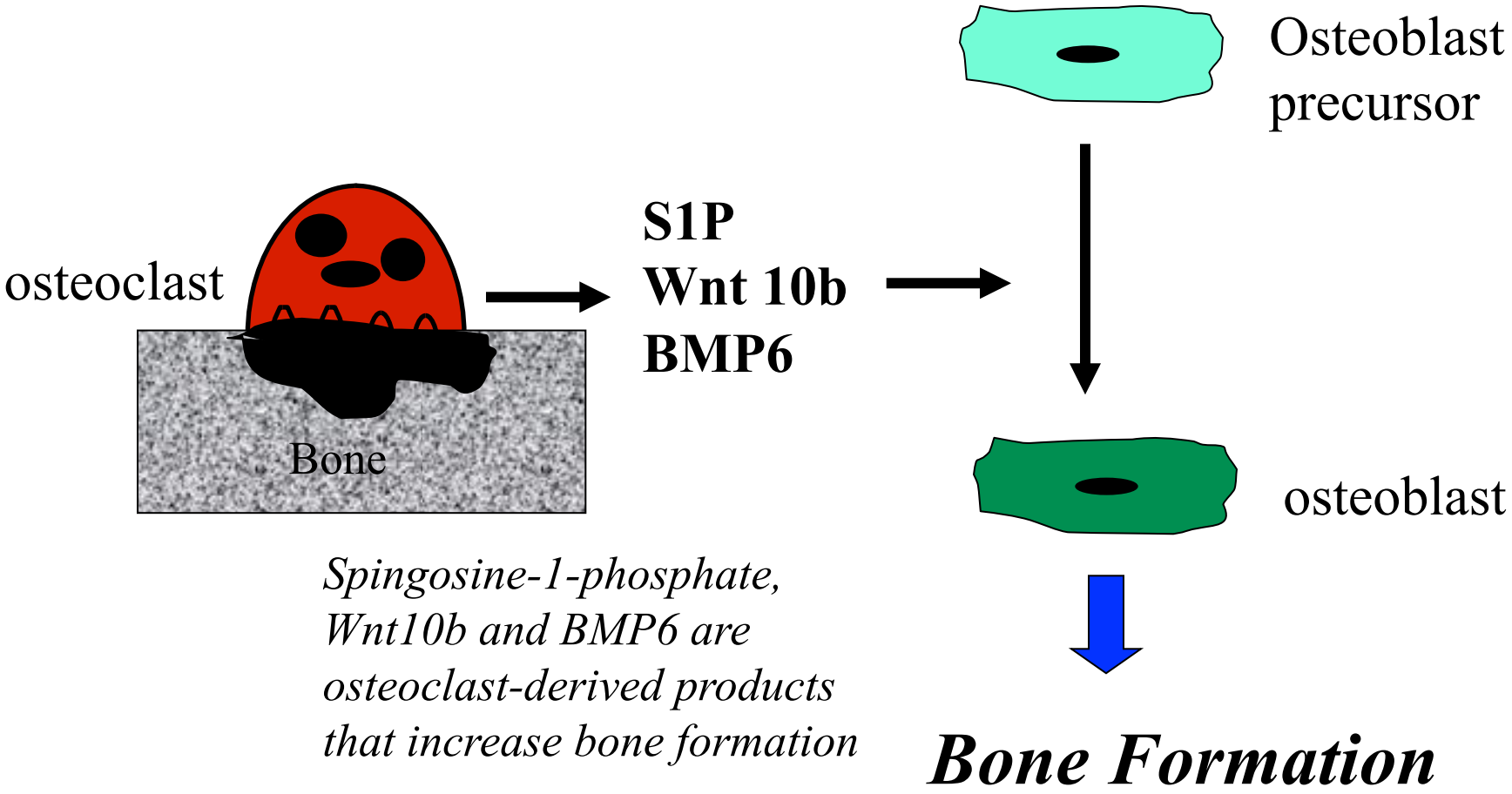
Physiologic Bone Remodeling

Mechanisms of coupling of bone resorption and formation



Products released from the bone matrix activate osteoblast-mediated bone formation

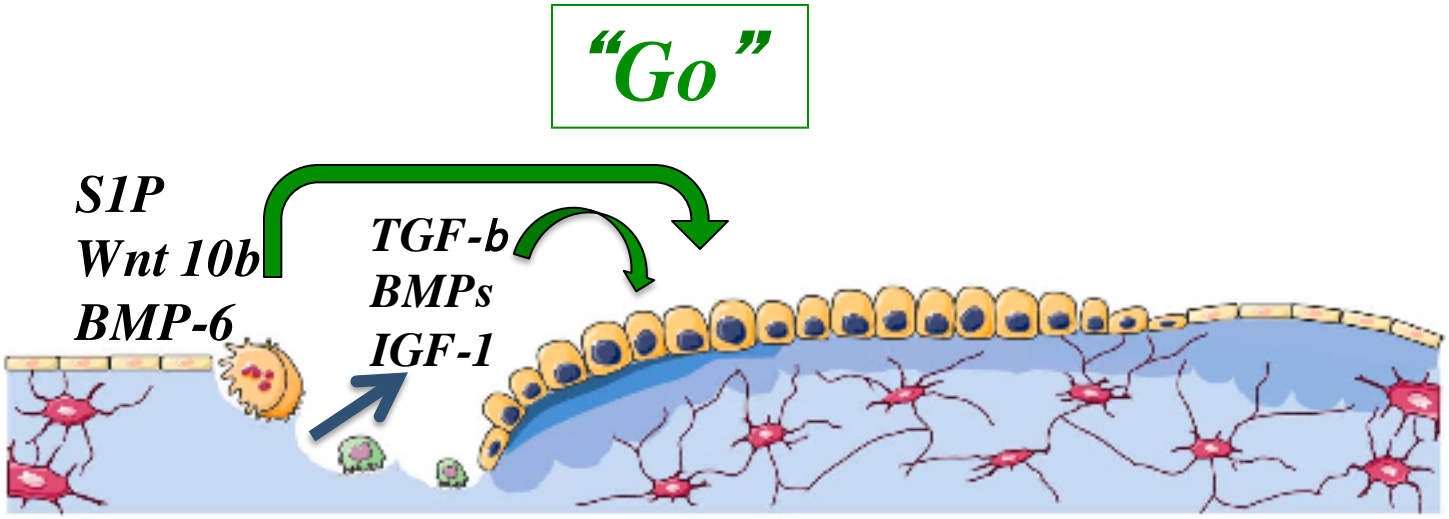
Osteoclasts produce factors that stimulate bone formation



Spingosine-1-phosphate, Wnt10b and BMP6 are osteoclast-derived products that increase bone formation

Pederson L et al. PNAS 2009; 105:20764-20769
Masuzaki E et al. Bone 2013; 55:315-24
Purdue E, Goldring SR, McHugh K. 2014; Sci Rep. 2014;23;4:7595

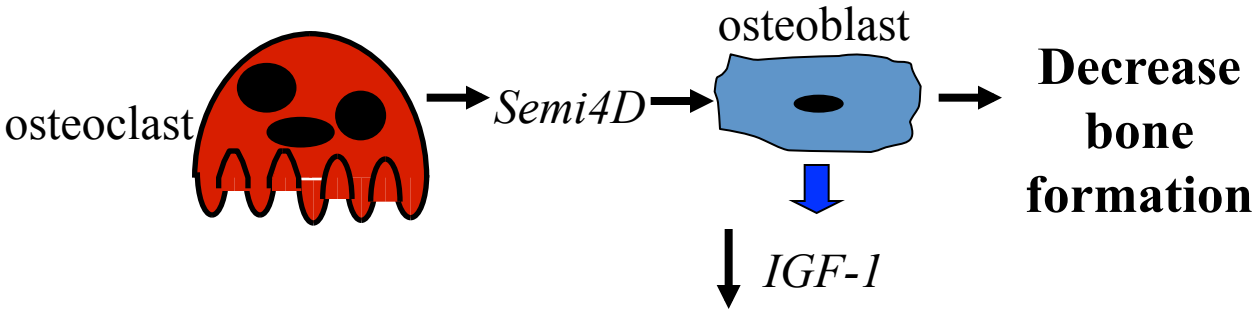
Mechanisms of coupling of bone resorption/ formation

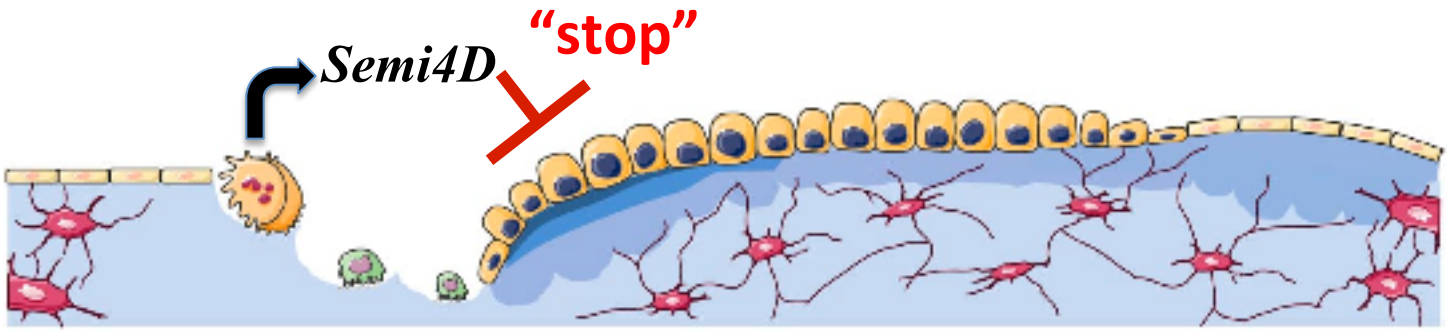


Osteoclast-derived products contribute to coupling of bone resorption and formation

During osteoclast-mediated bone resorption, osteoclasts also produce factors that block the initiation of bone formation

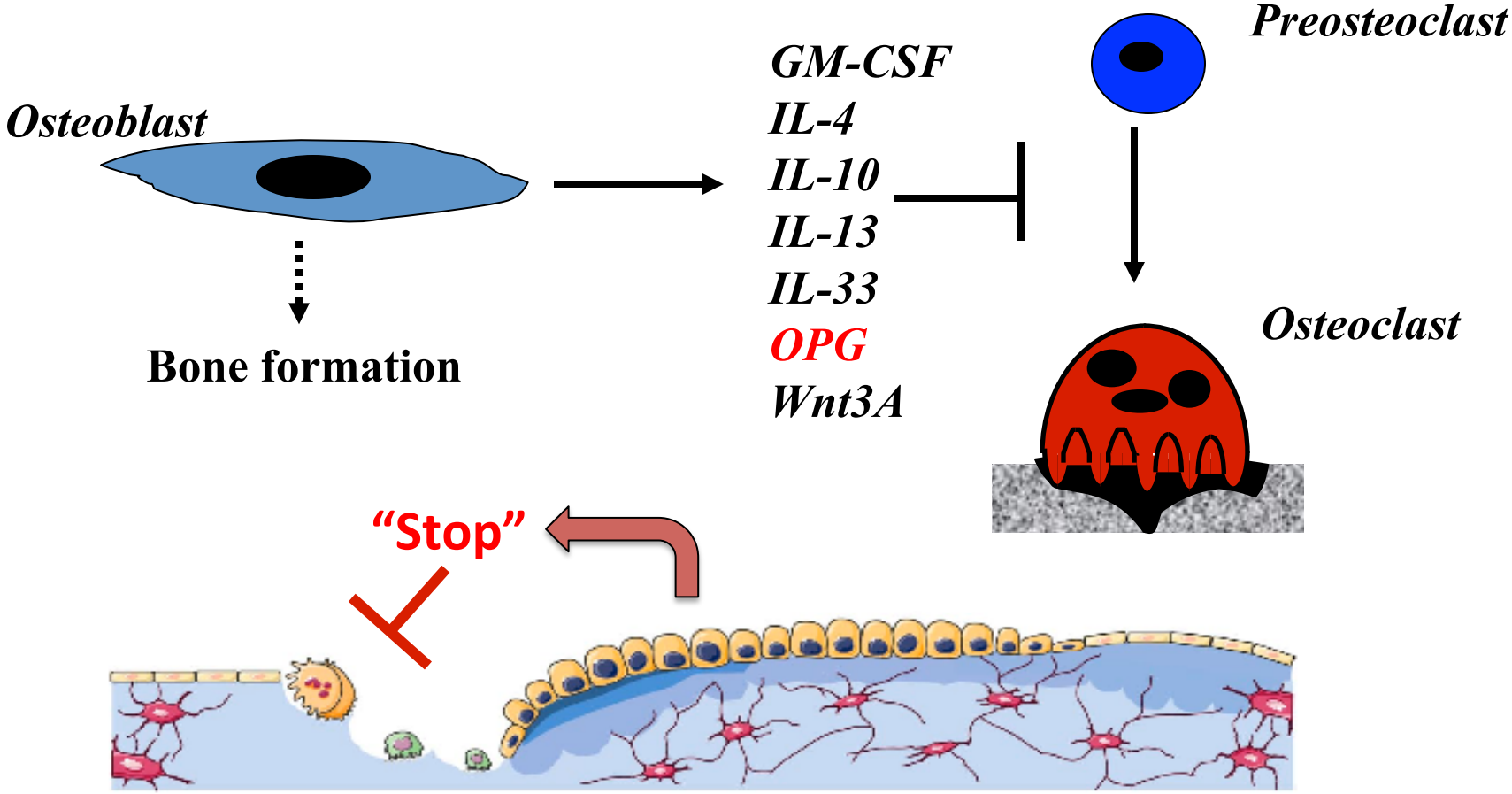
- *Osteoclast–derived products provide "stop" signals*





Negishi-Koga T et al. Nat Med 2011; 17:1473-81

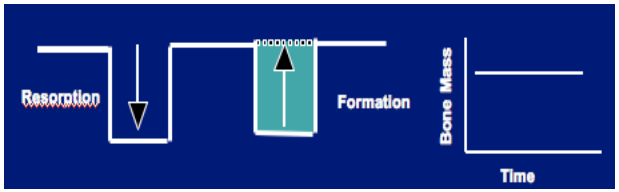
Osteoblasts provide "stop" signals to osteoclasts

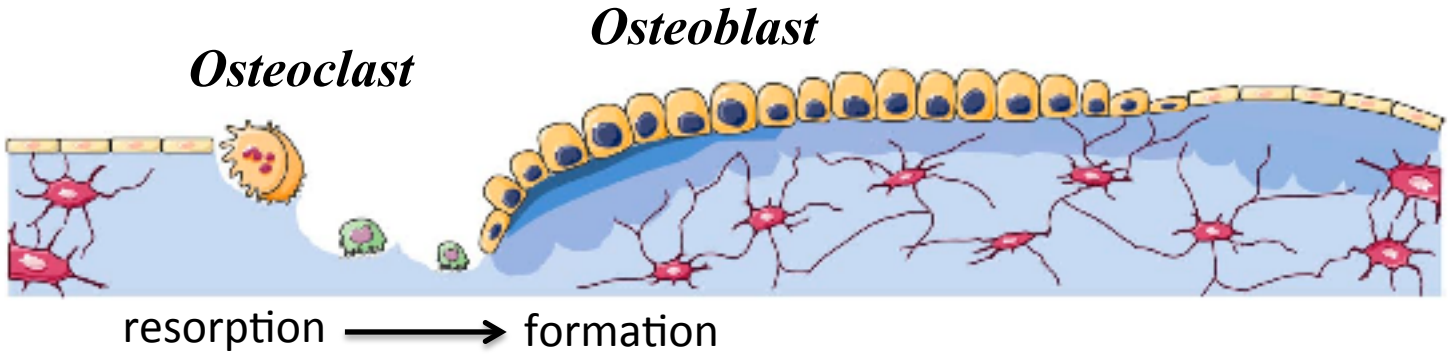


Schulze et al. JBMR 2011;26:704-17;
Zaiss et al. J Immunol 2011; 186:6097-105
Keller et al. BBRC 2012; 417:217-22
Maeda K et al. Nat Med 2012; 18:405-13

Physiologic Bone Remodeling

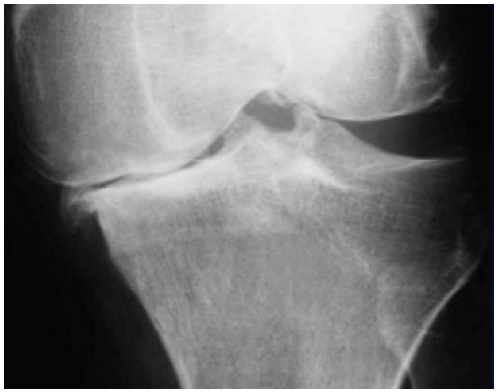
- Adapt shape and structural organization to alterations in ***biomechanical forces***
- Maintain structural integrity
  - Repair microdamage
- Maintain mineral ion homeostasis

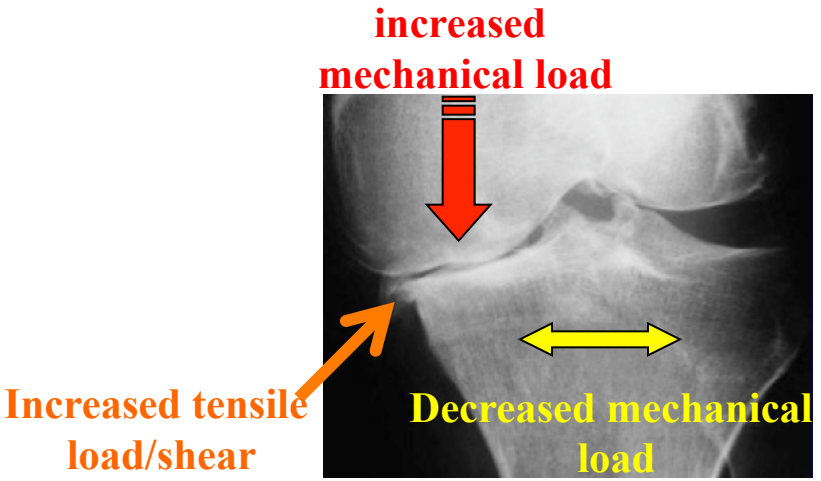




Question: How is the remodeling process regulated by biomechanical forces?

Role of biomechanical factors in periarticular bone adaptation in osteoarthritis





- Increased cortical plate thickness
- Flattening and deformation of articular contour
- Decreased subchondral trabecular bone mass
- Osteophyte formation

- Modeling and remodeling
- Remodeling
- Remodeling ("stress-shielding")
- Endochondral bone formation

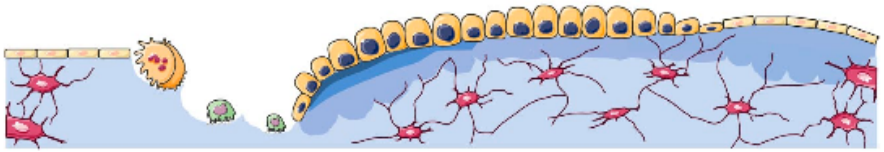
Periarticular bone changes reflect adaptation to local biomechanical forces and the alterations are mediated by cellular mechanisms: ***"Wolff's law"***

- *Increased load=increased mass*
- *Decreased load=decreased mass*

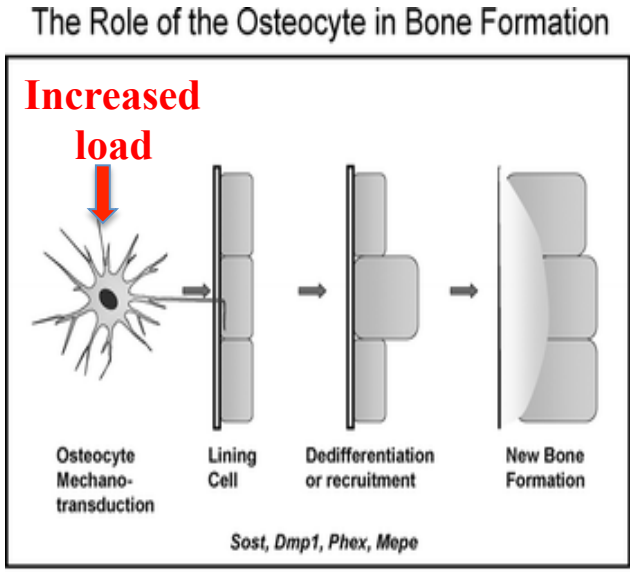
Question: What are the cellular mechanism involved in the adaptation?

Mechanism of bone adaptation to local mechanical influences

The *osteocyte* is mechano-sensor of bone

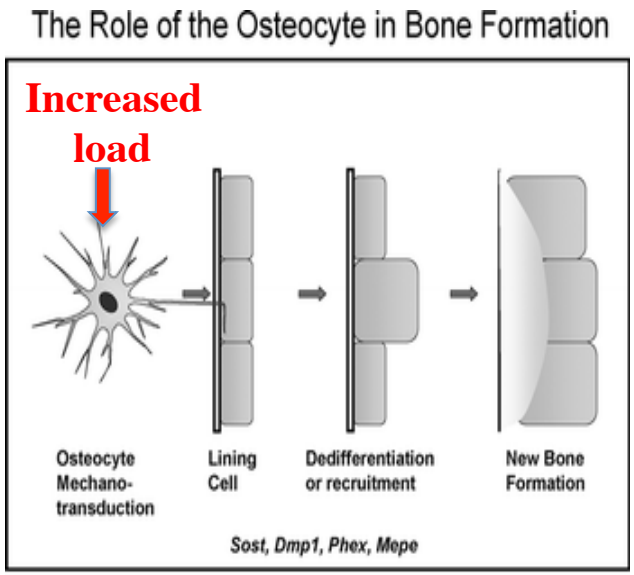


- **The osteocytes form a syncytium within bone.**
- **Their interconnected network is in contact within the cells on the bone surface and with each other.**
- **Osteocytes regulate bone remodeling and modeling through interaction with osteoblast and osteoclasts (and their precursors) via direct cell-cell communication and by the release of soluble mediators.**

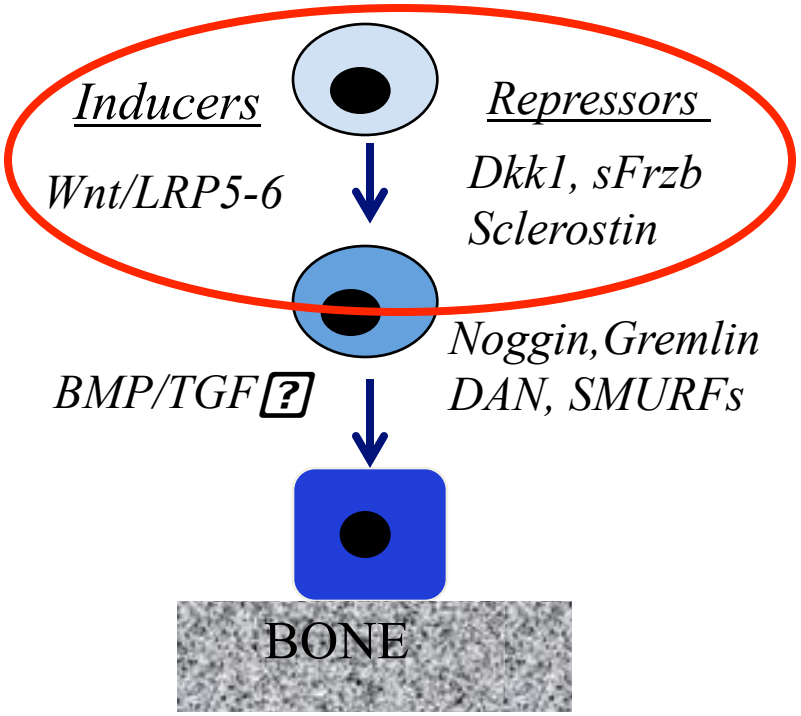


From the *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, 7th Edition*. www.asbmrprimer.org

What are the mechanisms responsible for load-induced increases in bone formation?

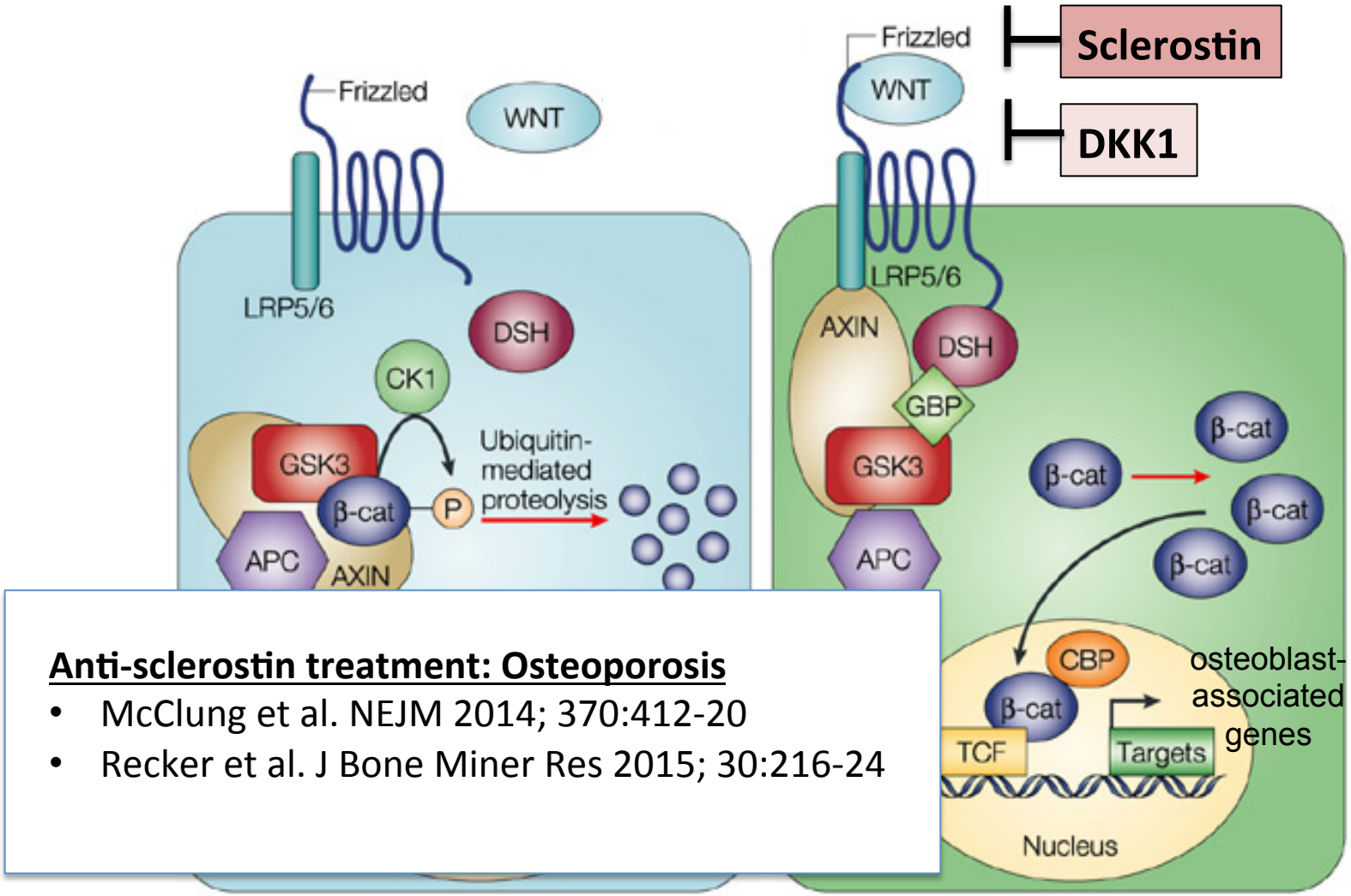


Regulators of osteoblast-mediated bone formation



Osteocytes regulate bone formation by production of molecules that control osteoblast differentiation and activity

Binding of Wnt(s) activates Wnt/[?]-Catenin signaling pathway



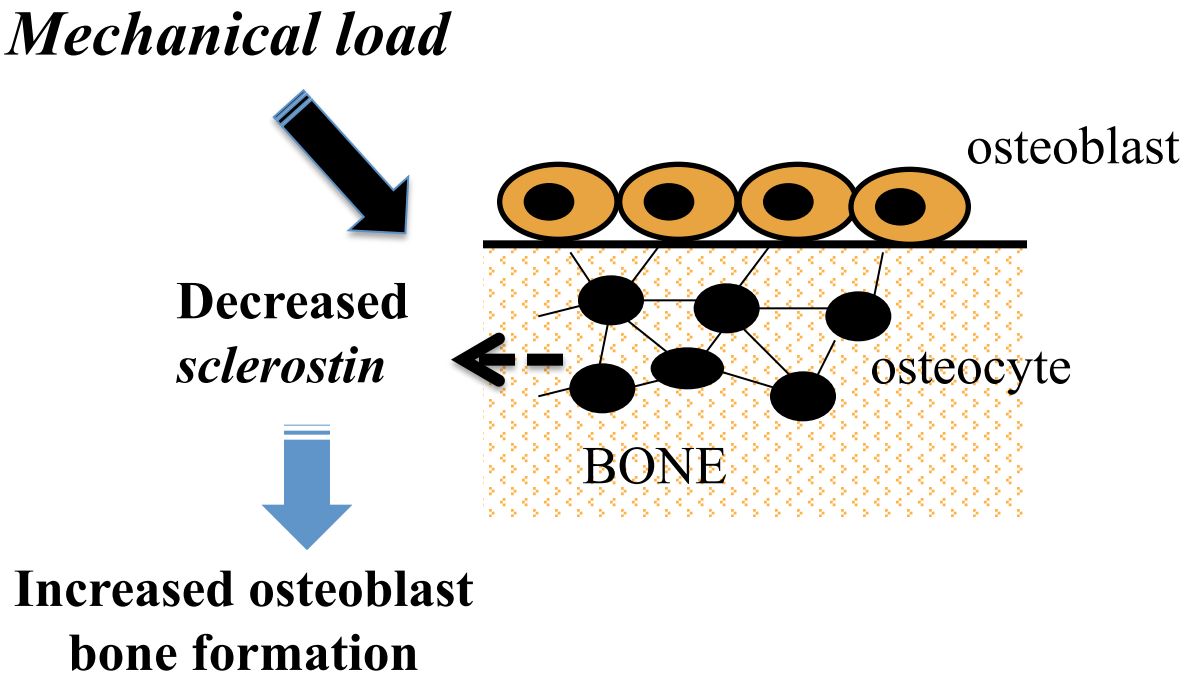
Anti-sclerostin treatment: Osteoporosis

- McClung et al. NEJM 2014; 370:412-20
- Recker et al. J Bone Miner Res 2015; 30:216-24

Moon RT et al. 2004; 5:689-99 z

Nature Reviews | Genetics

Osteocyte-derived sclerostin modulates bone formation



- ***Inhibiting sclerostin increases bone formation***

Bellido T et al Endocrinology. 2005; 146:4577-83
Robling AG et al. JBC; 2008;283:586-75

Physiologic Bone Remodeling

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- Maintain structural integrity
  - Repair microdamage
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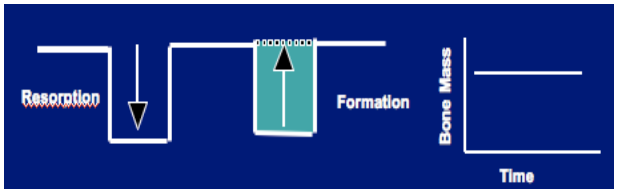
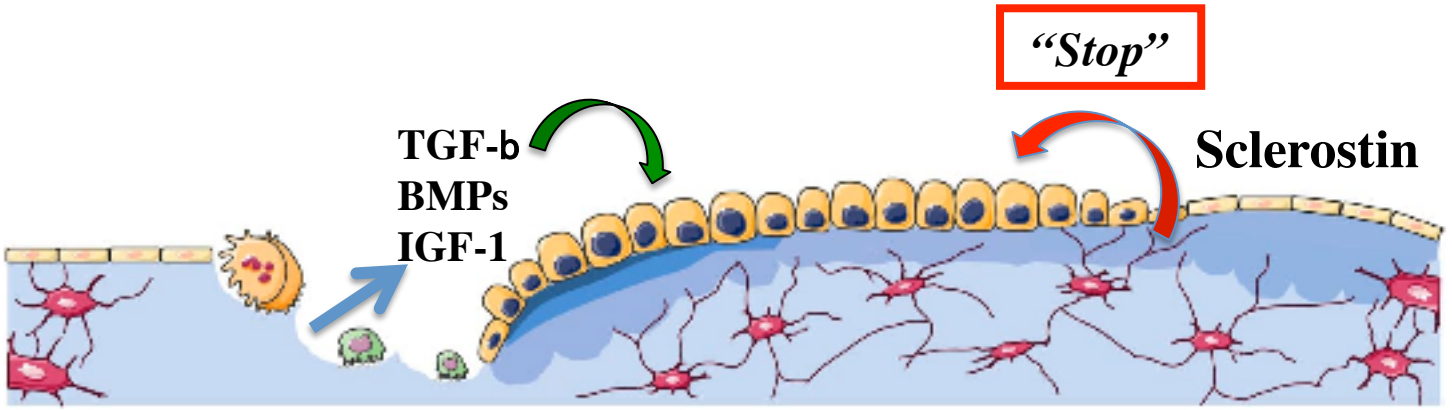
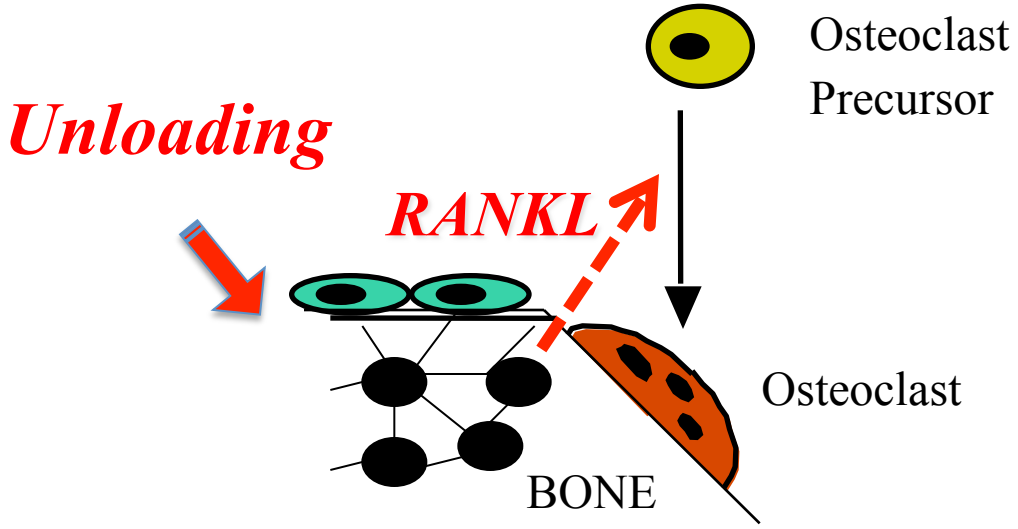




Osteocyte-derived sclerostin provides a "stop" signal for terminating bone formation in a bone remodeling unit

Increased load decreases sclerostin and increases bone formation

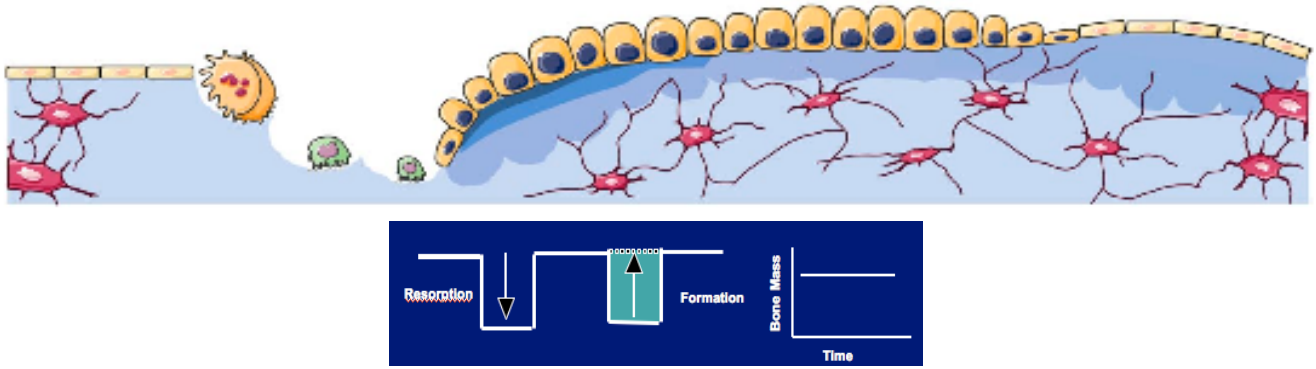
Role of osteocytes in regulation of osteoclast-mediated bone resorption



- **Osteocytes up-regulate RANKL in response to unloading**
- **Osteocytes via *RANKL* or *sclerostin* production regulate adaptation of bone to mechanical (and hormonal) signals**

-Xiong et al. Nat Med 2011; 17:1235-41
-Nakashima et al. Nat Med 2011; 17:1231-34

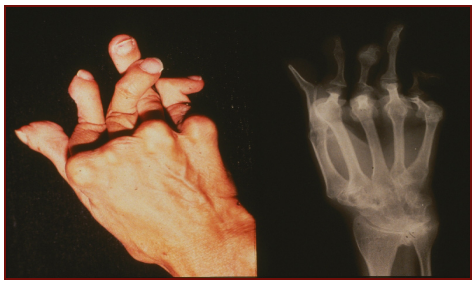
Factors involved in regulating bone remodeling and coupling



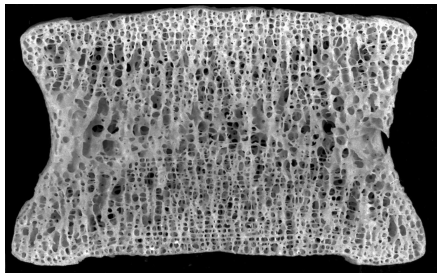
Resorption=Formation

- Bone matrix derived products (BMPs, TGF-b, IGF-1)
- Cell-derived products
  - Osteoclast (S-1-P, Wnt10b, BMP6)
  - Osteocyte (RANKL,OPG, Sclerostin, PGEs, NO)
  - Osteoblast (IL-4, IL-10, IL-13, IL-33,Wnt3A, OPG)
- **Mechanical factors**

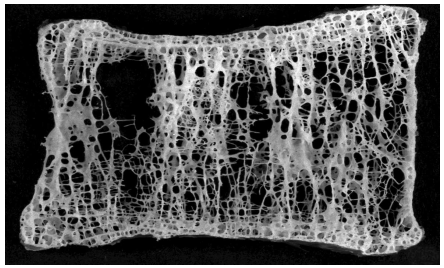
Rheumatoid Arthritis: a paradigm of pathologic bone remodeling



Normal vertebral body



Osteoporotic



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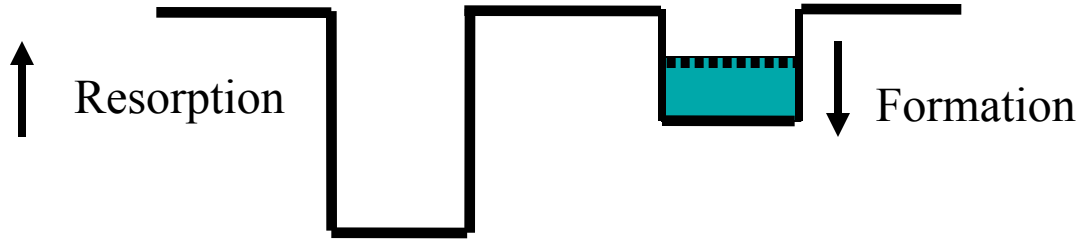
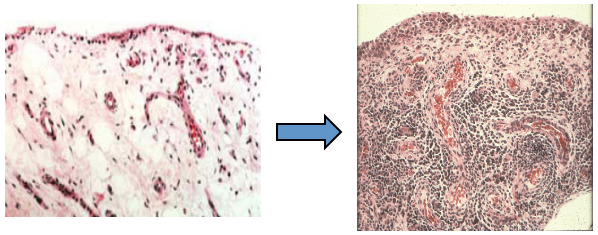
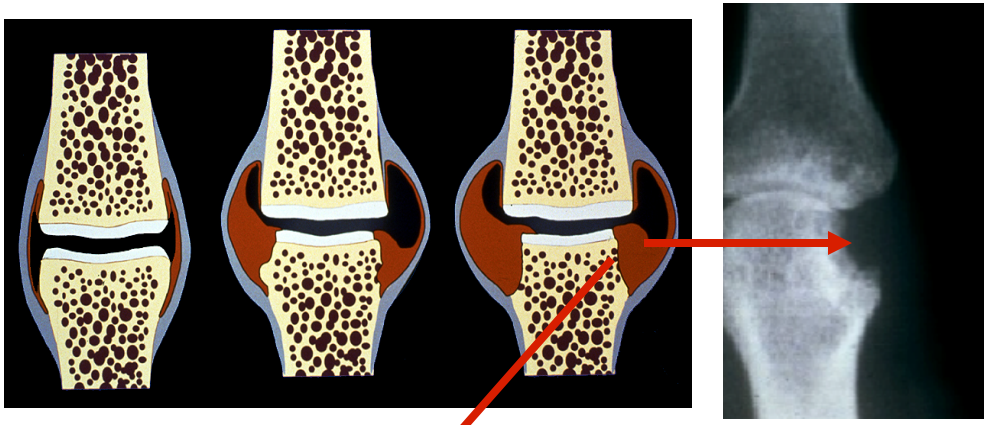


- **Bone resorption and formation are uncoupled**
- **What accounts for the uncoupling?**

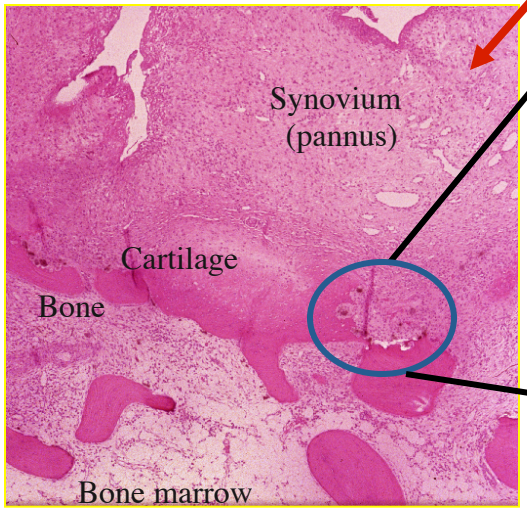
Marginal Joint Erosions in RA

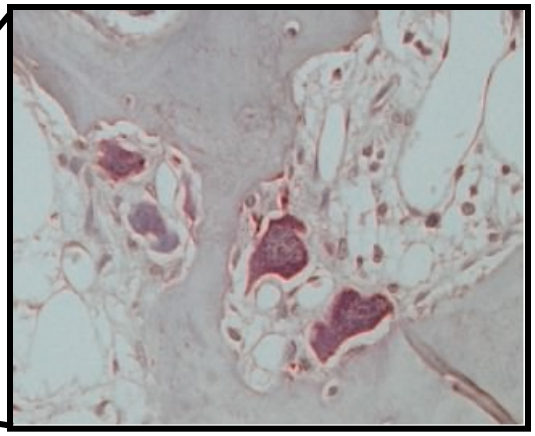


- *Synovial fibroblast hyperplasia*
- *Neovascularization*
- *Inflammation: T cells, B cells, macrophages, dendritic cells*



Inflamed synovium contains osteoclast precursors





Cells with phenotypic features of osteoclasts are present in resorption lacunae at the bone synovial interface.

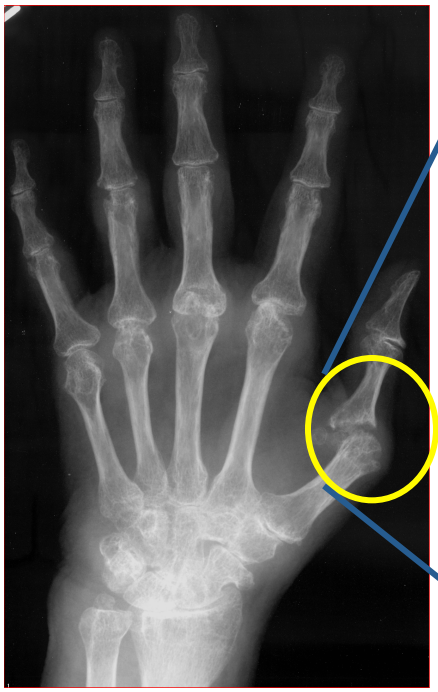
Takayanagi et al A&R 2000; 43: 259-69
Itonaga I et al J Pathol 2000;192:97-104
Haynes DR Rheumatology 2001; 40:623-30
Suzuki Y Rheumatology 2001; 40:673-82
Lubberts E Arthritis Rheum 2002; 46:3055-64

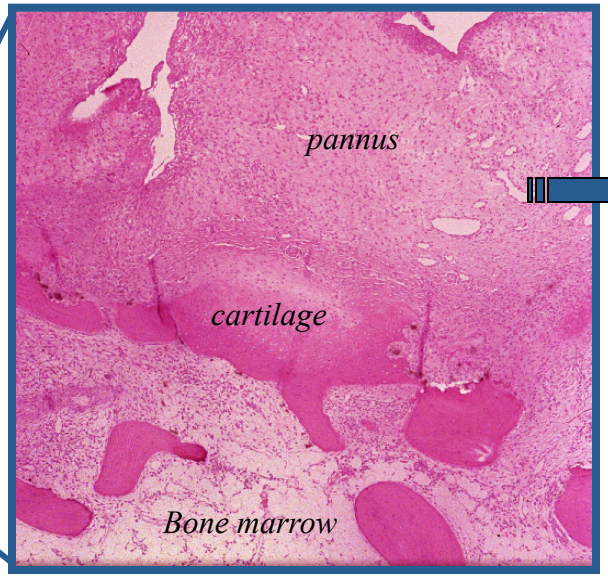
Genetic ablation of RANKL in a model of RA prevented bone erosions. *Osteoclasts are required for bone erosions*

Pettit, Goldring, Gravallese et al. Am J Pathol 2001; 159:1689-1699

Gravallese, Goldring et al. Am J Pathol, 1998; 152:943-951

Immunomodulatory and proinflammatory factors produced by RA synovium with osteoclastogenic activity





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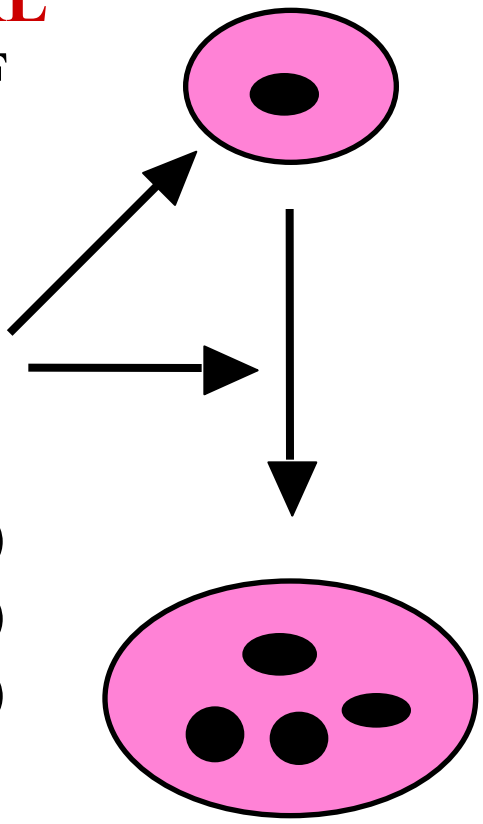
Macrophage lineage cell

RANKL
M-CSF
TNF-a
IL-1
IL-6
IL-11
OSM
(IL-15)
(IL-17)
(IL-23)



Osteoclast

Denosumab treatment effects on structural damage, bone mineral density and bone turnover in RA

A 12 month, multicenter, randomized, double-blind, placebo-controlled phase II clinical trial

-Decrease in progression of MRI erosions

-Decrease in progression of Sharp erosion scores

-Sustained suppression of bone turnover markers

-Positive effect BMD

-No effect JSN

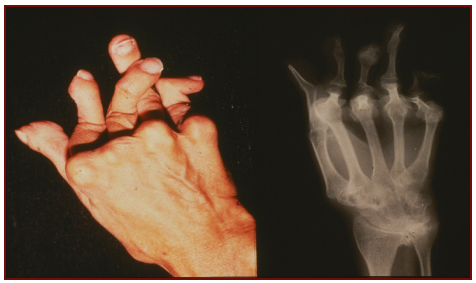
-No effect disease activity

-No difference in adverse events

Conclusion: *RANKL* blockade inhibits osteoclastic bone resorption and inhibits the development of bone erosions

Cohen et al. Arthritis Rheum 2008; 58:1299-1309

Rheumatoid Arthritis: a paradigm of pathologic bone remodeling



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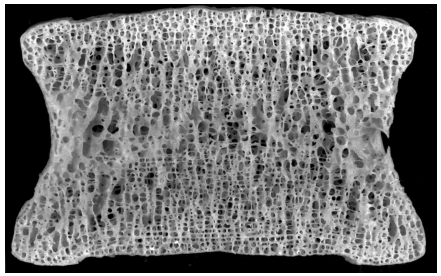

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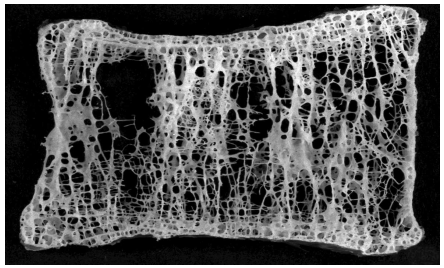

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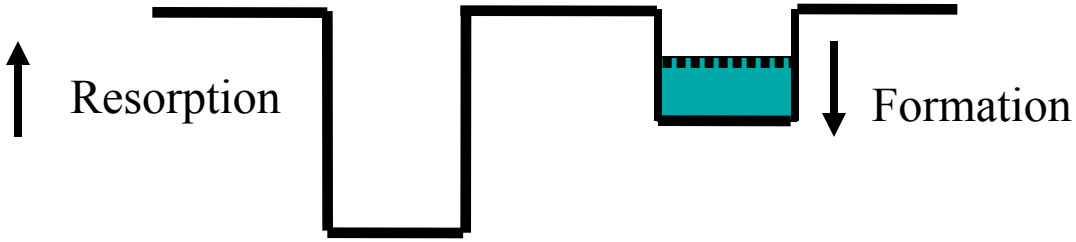
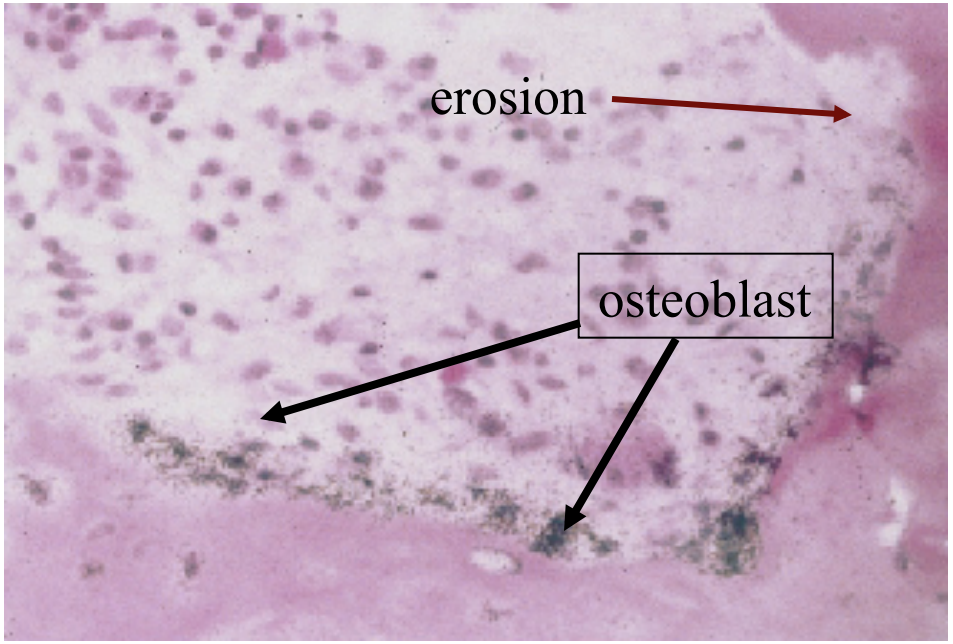


Bone resorption and formation are uncoupled

What accounts for the bone formation defect?

Osteoblast-like cells at sites of bone erosions express PTH receptors

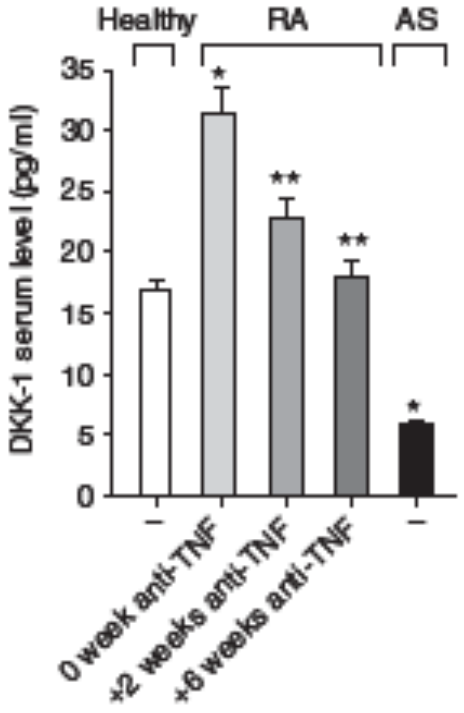


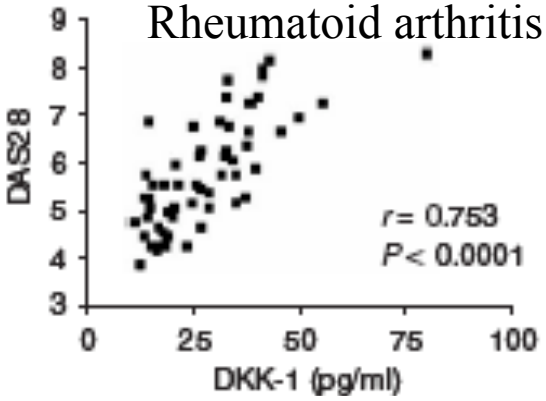
Despite the presence of osteoblasts in regions of focal bone erosions, there is defective bone formation.

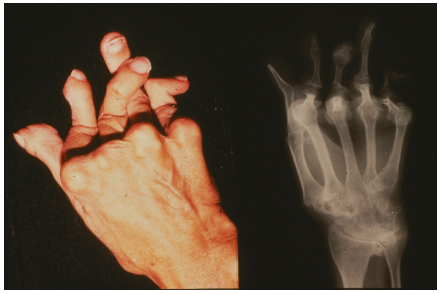
-Gravallese EM, Goldring SR et al. Am J Pathol, 1998; 152: 943-951

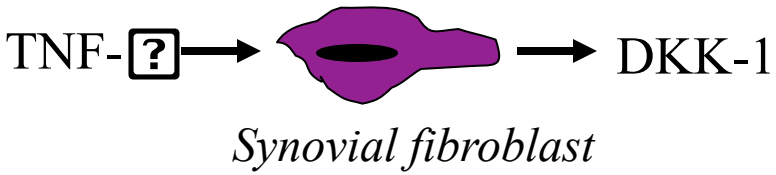
-Walsh N, Burr DB, Gravallese et al. JBMR, 2009;24:1572-85

Role of DKK-1 in suppression of bone formation in inflammatory arthritis





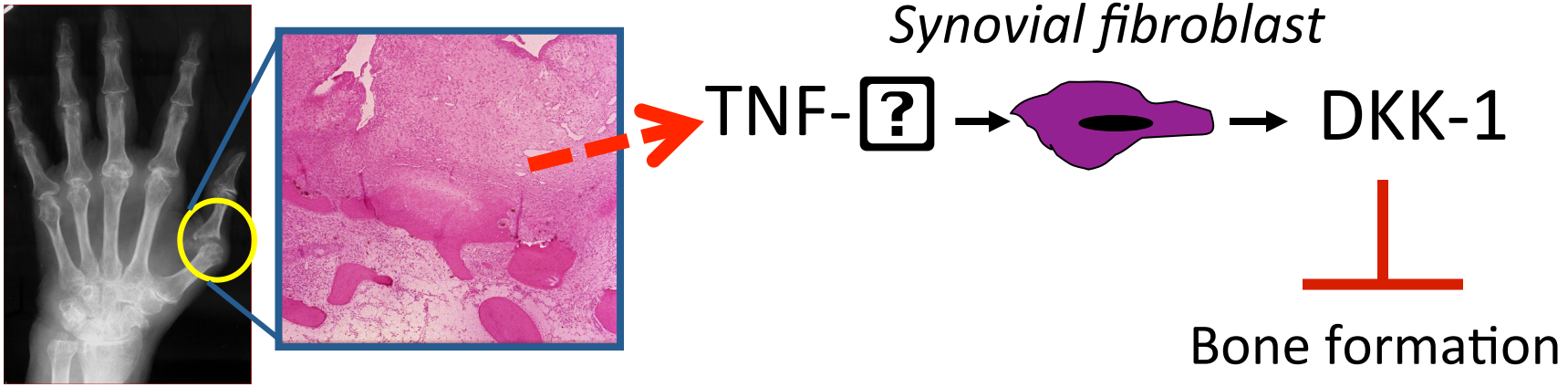




Synovial fibroblast

Diarra et al. Nat Med 2007; 13:156

TNF-a induces DKK-1 in RA synovial fibroblasts



- **Monocyte- and T cell-derived TNF−a induces DKK-1 by synovial fibroblast**
- **DKK-1 inhibits bone formation**

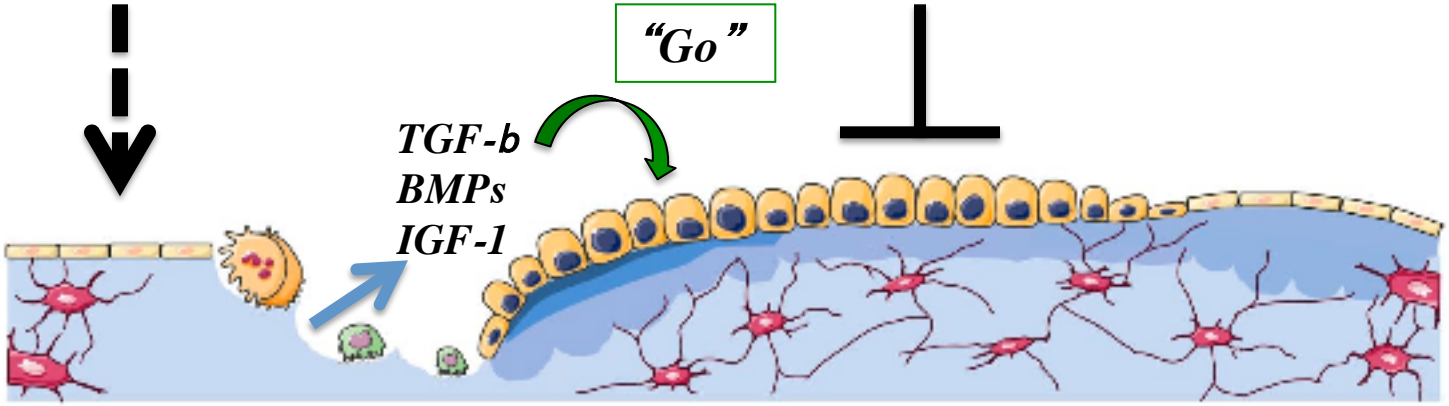
Diarra et al. Nat Med 2007; 13:156

Uncoupling of bone formation in RA

Inflammatory arthritis
Pro-osteoclastogenic factors

Rheumatoid Arthritis

DKK-1
Sclerostin



Increased osteoclastic resorption

Decreased bone formation

Role of DKK-1 in supression of bone formation in inflammatory arthritis

- **DKK-1 levels elevated in serum and synovial tissue from RA patients**

- **TNF induces DKK-1 in synovial fibroblasts**

- **Treatment of animals with inflammatory arthritis (TNF-transgenic, collagen-induced arthritis or serum transfer arthritis) with a DKK-1 blocking antibody preserved bone formation.**

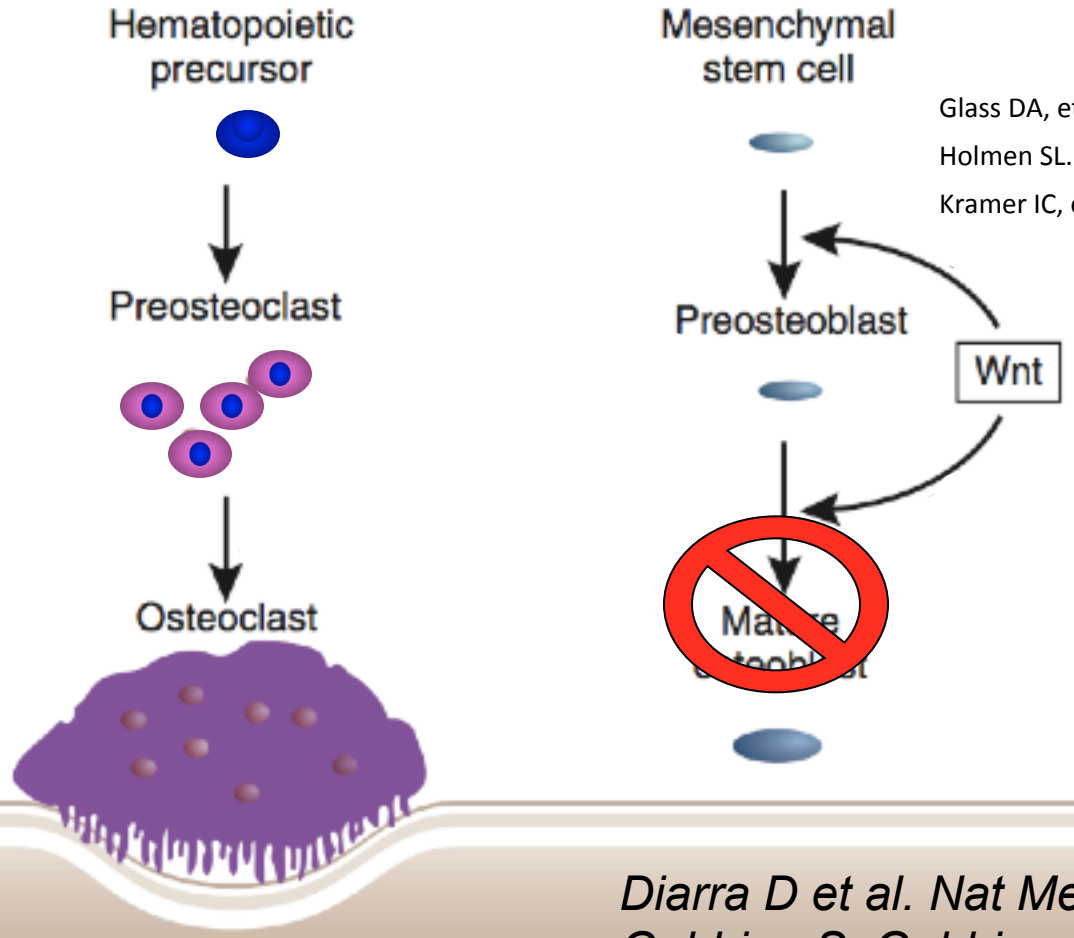
Diarra et al. Nat Med 2007; 13:156

-DKK-1 inhibits bone formation in inflammatory arthritis

-DKK-1 enhances bone resorption in inflammatory arthritis

-Inhibition of DKK-1 restores bone formation

-Inhibition of DKK-1 increases OPG and decreases bone erosion



Glass DA, et al. Dev. Cell. 8:751-764. 2005

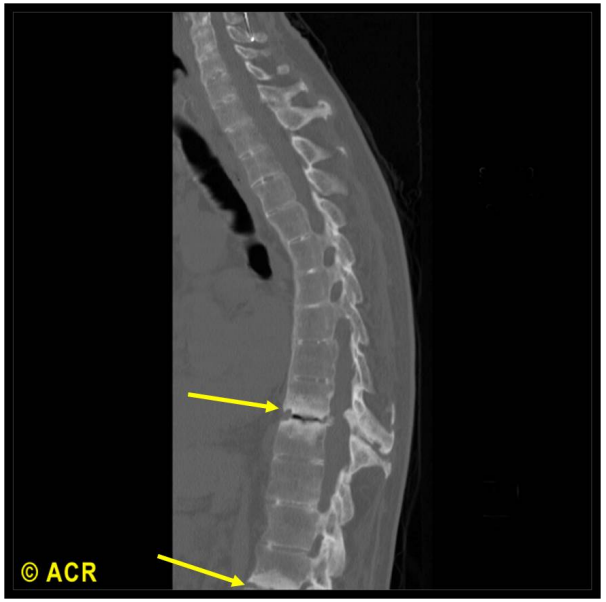
Holmen SL. JBC 280: 21162-21168. 2005

Kramer IC, et al. Mol. Cell. Biol. 30: 3071-3085. 2010

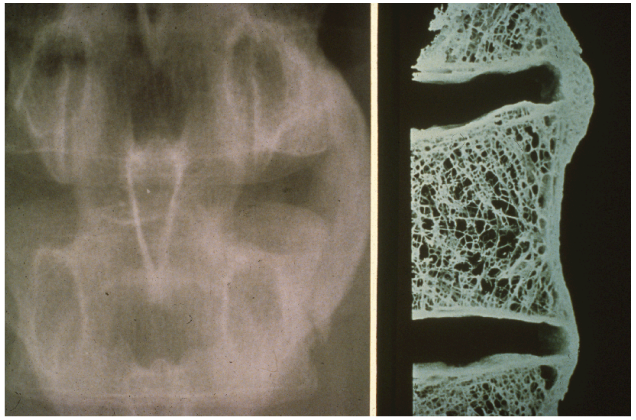
Diarra D et al. Nat Med 2007; 13:156-163

Goldring S, Goldring M.. Nat Med 2007; 13:133-

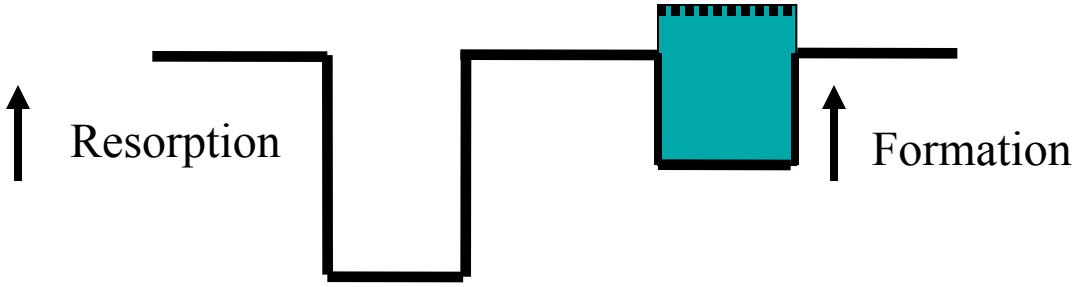
Uncoupling of bone resorption and formation in ankylosing spondylitis



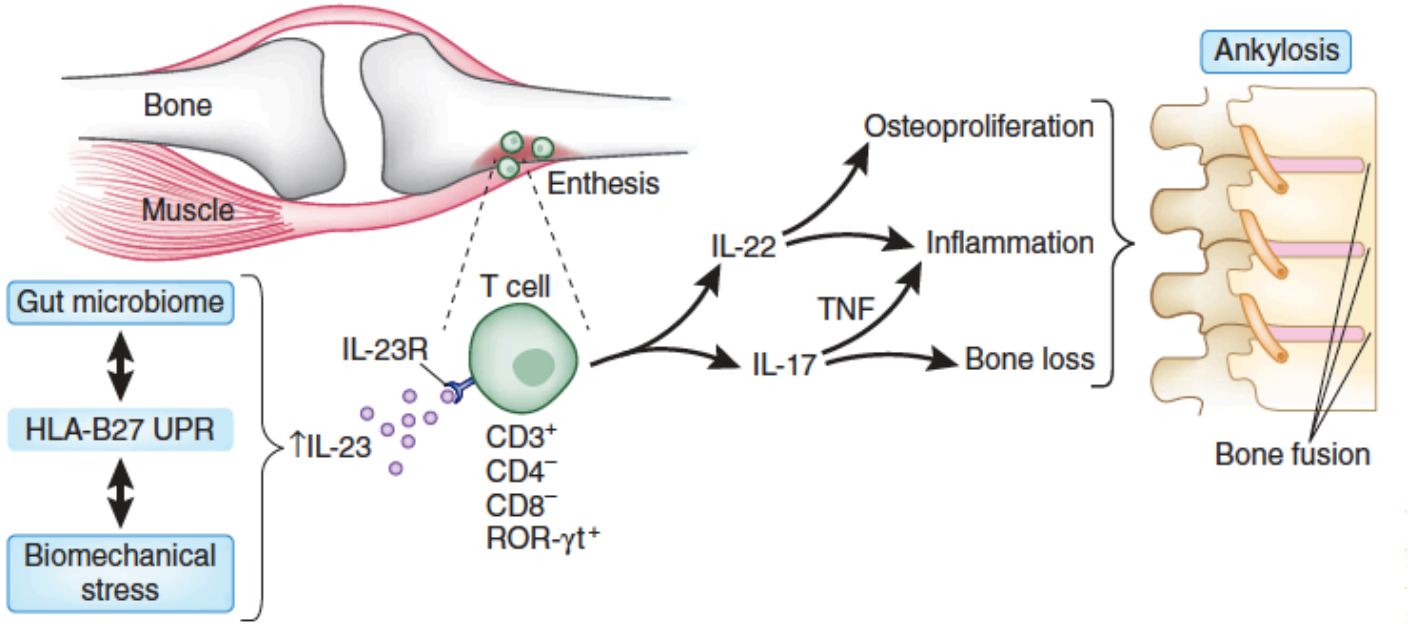
CT demonstrating focal erosion and "sclerosis"

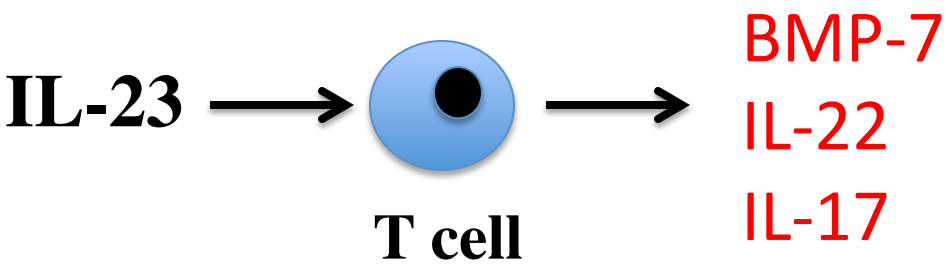


Syndesmophytes



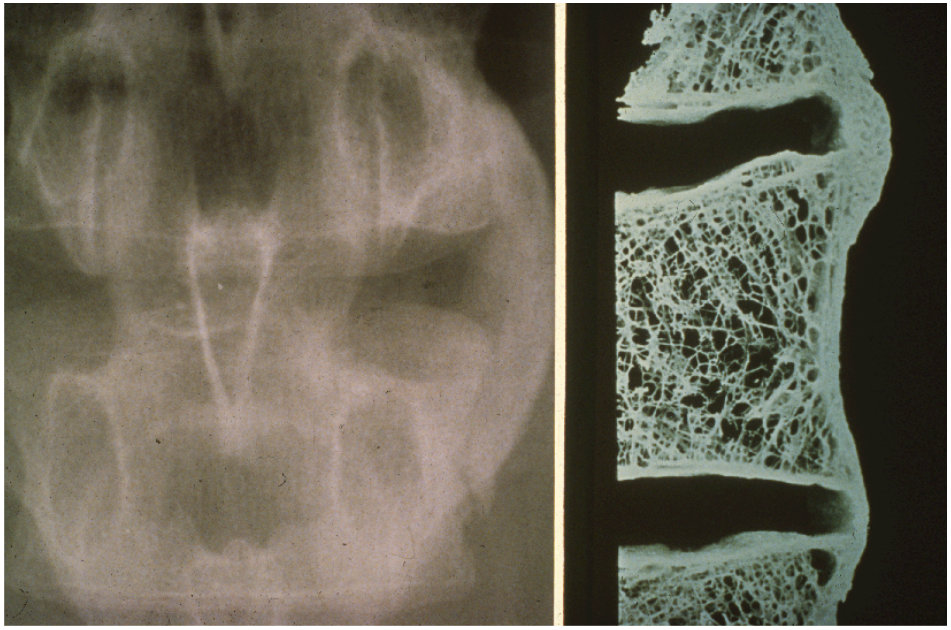
Role of IL-23 interaction with T cells in entheseal inflammation





Sherlock JP et al. Nat Med 2012; 18:1069-76
Lories RJ, McInnes IB. Nature Med 2012;18:1018-9

Putative mechanisms of increased bone formation in AS



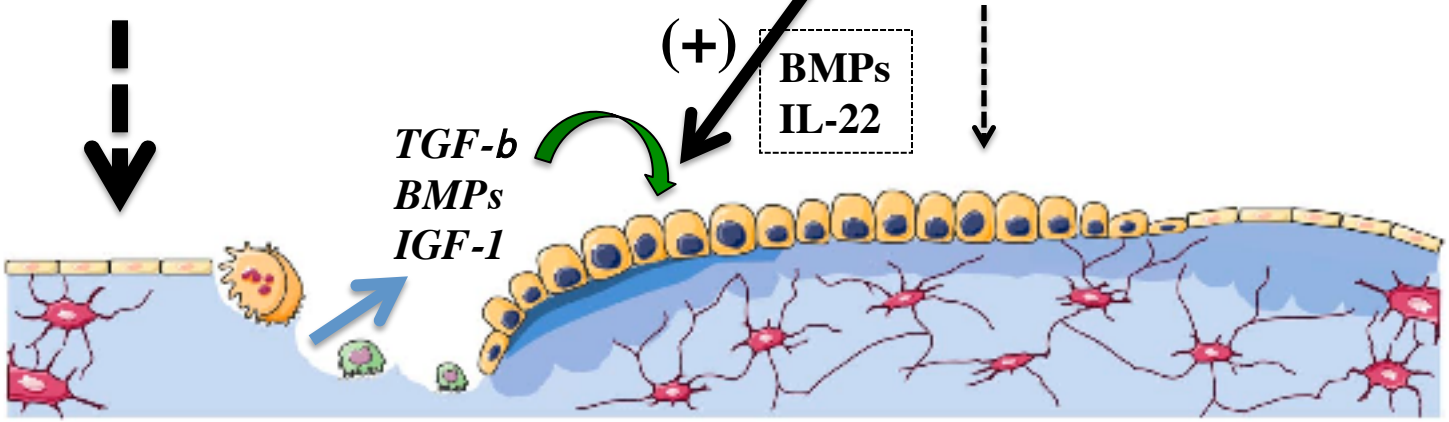
- Reduced expression sclerostin and DKK-1 in tissues and serum
- Increased levels of TGF-? in human SI joint and increased BMP expression in synovial and enthesial tissues in animal models of AS
- Blockade of DKK-1 induces SI joint fusion in animal model of AS

Lories RJU et al. ARD 2004; 63:595-8
Lories RJU et al. JCI 2005; 115:1571-9
Francois RJ et al. ARD 2006; 65:713-20
Lories RJU et al. A&R 2006; 54:1736-46
Appel H, Schett G et al. A&R 2009; 60:3257-62
Uderhardt S et al. ARD 2010; 69:592-6

Uncoupling of bone formation in AS

Inflammatory arthritis
Pro-osteoclastogenic factors

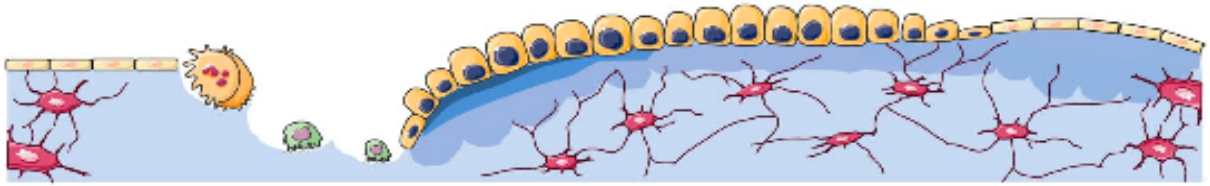
Ankylosing Spondylitis
(absence of DKK1/sclerostin)



Increased osteoclastic resorption

Increased bone formation

Factors involved in regulating bone remodeling and coupling



- Bone matrix derived products (BMPs, TGF-b, IGF-1)
- Cell-derived products
  - Osteoclast (S-1-P, Wnt10b, BMP6)
  - Osteocyte (RANKL,OPG, Sclerostin, PGEs, NO)
  - Osteoblast (IL-4, IL-10, IL-13, IL-33,Wnt3A, OPG)
- Mechanical factors
- **Pathological states**
  - **Synovial fibroblasts**
  - **Immune cells (T cells, B cells, dendritic cells)**

Summary

- **Many of the rheumatic diseases are associated with de-regulated bone remodeling**

- **Products generated by the inflammatory process deregulate the activity and function of bone cells that remodel and adapt the bone under physiological conditions**

- **Biological as well as biomechanical factors contribute to the de-regulation**

- **An understanding of the cellular and molecular mechanisms involved in the de-regulated bone remodeling provides a unique opportunity to develop novel and improved therapies for treatment of disorders of pathologic bone remodeling**