PATHOPHYSIOLOGY of OSTEOPOROSIS: Pathways That Control Bone Remodeling

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TOPICS

- Bone remodeling and modeling
  - Imbalances underlie bone loss, repair
- Resorption – RANK-L/RANK/OPG
- Formation - Wnt/LRP5/Beta catenin
- Pathogenesis of bone loss (menopause, age)
  - Immune mediators, microbiome – estrogen deficiency
  - “Coupling hypothesis” - resorptive function and signaling pathways of osteoclasts regulate osteoblast function

Why Do Bones Remodel?

Allows skeleton to --
- Respond to mechanical loading (modeling)
- Repair microdamage (“wear and tear”) & prevent accumulation
  - Maintains “quality control”

BONE REMODELING – process of coupled resorption and formation that maintains bone mass in adult life (10%, slow)

BONE MODELING – process that shapes bones as we grow & develop (childhood, adolescence); also occurs at low rate throughout life, resorption and formation are uncoupled, and they occur on different surfaces (basis for anabolic therapies)

Microfracture Is Repaired through Targeted Remodeling

Segovia-Silvestre T et al, Hum Genet, 2009
**Why Do Bones Remodel?**

*Allow skeleton to --*

- Respond to mechanical loading (modeling)
- Repair microdamage ("wear and tear") & prevent accumulation
- Maintains “quality control”
- Release minerals (Ca and phosphate) & growth factors stored in matrix into circulation
- Important in skeletal homeostasis (role in remodeling imbalance of age)

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**RANK-Ligand/ RANK/ Osteoprotegrin Pathway**

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**Osteoclastogenesis: Hormones, Growth Factors, Cytokines Stimulate Expression of RANK-L (RANK+RANK-L Interact)**

![Diagram of Osteoclastogenesis]

**Osteoprotegerin (OPG) Prevents RANK-L/ RANK Interaction & Inhibits OC Activity [OPG=Circulating Inhibitor]**

![Diagram of Osteoprotegerin Pathway]

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**OSTEOBLAST LINEAGE CELLS**

Mesenchymal stem cells, pre-OB’s, mature OB’s, bone-lining cells, stromal cells, and osteocytes

- Produce matrix and mineralize it –
  - Mechanical support
  - Matrix - reservoir of Ca, phosphate, growth factors, hormones
  - Secrete endocrine & paracrine factors – FGF23, DMP1, etc
- Modulate development of tri-lineages of blood cells
- Play role in metabolism, male reproduction

Function and numbers of cells in OB lineage decline with aging – many factors responsible

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**Bone Formation**

LRP5/Wnt/β-Catenin
**Canonical Wnt Signaling**

Lewecki et al, Nat Rev Rheumatol, 2011

**Wnt Inhibition**

- **WIF1** (Wnt inhibitory factor) or **SFRP** (secreted frizzled related protein) sequester Wnt ligand
- then, **Axin** & **APC** associate with **GSK-3β** increase phosphorylation of **β-catenin**
- **β-catenin~P** → ubiquitinated → proteasome for degradation
- **NO bone made**
- Other inhibitors: **N-cadherin** inhibits LRP5/6, **sclerostin** & **DKK1**

Baron R, Kneissel M, Nat Med 2013

**Sclerostin Secreted by Osteocytes Negatively Regulates Bone Formation**


- Loss of function mutations → **HIGH** bone mass
- Targeting therapy to neutralizing Scl (Mab)

**Sclerostin Inhibits Wnt Pathway**

*Neutralizing MAb to sclerostin


**Loss of Function Sclerostin Mutations**

- Both SOST/sclerostin genes mutated
- **SCLEROSTOSIS**
  - Child (A), adult (B,D) with SCLEROSTOSIS
  - Adult (C) healthy with dense bone, elevated BMD T- and Z-scores (spine, hip) – no fractures or deformities (over lifetime)

Gardner JC, et al, JCEM, 2005
**Comparison of Sequence Identity**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Ablaparatide design</th>
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<tbody>
<tr>
<td>hPTH</td>
<td>Abaloparatide analog that favored binding to R&lt;sup&gt;G&lt;/sup&gt; form of PTH-receptor ('biased agonist')</td>
</tr>
<tr>
<td>hPTHrP</td>
<td>Abaloparatide analog that favored binding to R&lt;sup&gt;G&lt;/sup&gt; form of PTH-receptor ('biased agonist')</td>
</tr>
<tr>
<td>ABL</td>
<td>Abaloparatide analog that favored binding to R&lt;sup&gt;G&lt;/sup&gt; form of PTH-receptor ('biased agonist')</td>
</tr>
</tbody>
</table>

**Abaloparatide**

*Novel analog of hPTHrP (1-34)*

- **Anabolic effects favored with strong peak responses but shorter overall cAMP signals**
- **Preclinical studies supported**

**Different ligands favor different PTH-R1 conformations (R<sup>P</sup> for PTH, R<sup>G</sup> for PTHrP)**

- *Anabolic effects favored with strong peak responses but shorter overall cAMP signals*
- *Preclinical studies supported*

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**Pathophysiology of Bone Loss**

**Menopause**

- Remodeling increases, more BMU’s are formed, deeper resorption pits (b)
- Amount of bone formed - less than what was resorbed
- Remodeling imbalance occurs (negative) - "uncoupling"
- With time - structural deterioration of bone
  - Thinned trabeculi, decreased connectivity, perforations

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**Effects of Estrogen on Bone Resorption**

- **Estrogen:** dampens IL-1, TNFα, decreases IL8, IL11, GM-CSF, RANKL, mCSF; increases OPG, TGF-β
- **Estrogen deficiency:** increases TNFα, IL1 → releases IL6, M-CSF, IL11, GM-CSF, RANKL → stimulates OC’s; decreases OPG, TGF-β

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**Gut Microbiome**

*Steves et al, JBMR, 2015*

- Billions of bacteria live in symbiosis with our bodies – influence health and disease
- Gut MB → host metabolic potential & innate & adaptive immune systems
  - Aging → Inflammation → Disease
- **Microbiome**
  - Role in osteoporosis, OA, gout, RA, sarcopenia, frailty
- **MODIFIABLE** - by probiotics (bacteria in food or dietary supplements) and prebiotics (usu complex CHO fibers in fruits/vegetables)
Gut Microbiome
(Hernandez CJ et al, JBMPI, 2016)

- Benefits to the host
  - Vitamin production (many)
  - Extracts nutrients and energy from diet
  - "Metabolic function" (metabolites → host)
  - Regulates immune system
  - Protects against pathogens getting in
- How might the microbiome help bone?
  - Enhance absorption of minerals (probiotics, prebiotics)
  - Enhance barrier function
  - Enhance immune system (good or bad)

A LOT OF EVIDENCE FOR MB INVOLVEMENT FOR BONE IN HUMANS - MOST IS INDIRECT

Gut MB May Play a Fundamental Role in Bone Mass Regulation (Igbal et al, JCI, 2016)

Normal gut flora antigens (in MB) are presented to APC, T cells
Pro-inflammatory cytokines made (ESTROGEN will normally dampen this, maintain barrier via gap junctions)

NO estrogen, these cytokines drive resorption systemically; barrier function also reduced (gap junctions – faulty)

Sex Steroid Deficiency (SSD) Associated Bone Loss Is Microbiota-Dependent and Prevented by Probiotics (Li et al, J Clin Inv, 2016)

- Female mice (SSD)
  - Gut permeability, expanded TH17 cells (OC-genic pop. T cells)
  - OC-genic cytokines in small intestine, marrow (TNF, RANK-L, IL-17)
  - Bone loss (micro-CT, histomorphometry, BTM's)

- Twice weekly treatment of SSD mice with probiotic
  - Reduced/transient/total/hormone bone loss (4 weeks after OVX)
  - No effects on cortical bone
  - Cytokines, T cell profiles (CD4), bone turnover are less pro-resorptive

- Probiotics improve trabecular BMD in control mice
- Several potential mechanisms postulated

Mechanisms for Age-related Bone Loss -

- Sex steroid def present (women, men) + nutritional issues (Ca & vitamin D def, often secondary HPT, sarcopenia)
- Intrinsic defects in marrow stromal cells with aging → impaired proliferation & differentiation ("senescent OB's")

More fat

**Age-related Osteoporosis**

- Imbalance in the bone formation response to ongoing bone resorption
- **Bone as tissue “ages”**
  - Changes in material properties – *affect strength* – and in matrix components – *affect constituents/composition* - released into microenvironment

Is the problem only with osteoblasts? Osteoclast lineage involved?

**Factors Released from Bone with Osteoclastic Resorption**

- IGF-1
- TGF-β
  - Promote bone cell proliferation, differentiation
  - TGF-β and IGF-1 levels in bone fall with age
  - Matrix changes with aging
  - May underlie reduced bone formation responses seen with aging in men and women

**Coupling Factor Hypothesis (OC→OB) - Osteoclast-Derived Factors**

- BMP6
- Wnt10b
- SCLEROSTIN
- S1P

**SIP/Rho GTPase Control of Osteoblast Lineage Cells**

- Sphingosine-1 Phosphatase
- RhoA GTPase
- Migration
  - Chemotaxis

**TGF-β Released From Bone Matrix During Resorption**

- CXCL16 chemokine
- LIF
  - Leukemia inhibitory factor

**TGF-β from OC Activity – Influences Migration of OB Cells**

- CXCL16 chemokine
  - Migration
  - Sites of Resorption
  - Fracture Repair
Osteoclasts Respond to TGF-β Released From Matrix During Resorption

Osteoclasts: Key Regulators of Bone Metabolism, Release ‘Coupling Factors’, Act Directly on OB’s — Process May Be Altered with Aging

Conditional Deletion of TGF-β Receptor II in Osteoclasts (mice)
(Weivoda et al, JBMR 31:76; 2016; provided by MJ Oursler)

• Bone mass reduced → trabecular osteopenia
• Bone weaker by mechanical testing
• OB numbers, serum P1NP, bone formation rates by histomorphometry (OB) - LOW
  Resembles senile bone loss

SUMMARY
• Sex hormone deficiency and age-related bone loss
  – Imbalances in remodeling, defects in coupling that favor net LOSS of bone mass
• Postmenopausal osteoporosis -
  – Altered cytokine milieu (bone, intestine)
  – Changes in T cell subpopulations (humans too)
  – Gut microbiome may be key
• Aging-related bone loss -
  – Defective OB function, "senescent" OB's
  – Altered communication of OC’s with OB’s
  – Changes in matrix composition (with aging) contribute