Bone: regulation of development and growth

Bone Modeling

Bone Remodeling
- Removal of damaged/aged bone by osteoclasts (microdamage)
- Replacement with new bone by osteoblasts (that become osteocytes)
- Process is linked: resorption followed by deposition (keeps bone strong)

Cell responsible for resorption: Osteoclast

Osteoclasts act to degrade bone. Here an osteoclast is eroding bone. The hollow formed by such action is called a Howship's lacunae (H). Similar to the cell of the gut, osteoclasts have a ruffled border which increases the surface area for bone resorption.

Intramembranous bone formation

- Occurs without a cartilage model (i.e., within a membrane only);
- Under high pO2, relatively undifferentiated mesenchymal cells become osteoblasts, and surround themselves with osteoid, which is then calcified (sound familiar?);
- Bone growth occurs by apposition.
- Examples:
  - Flat bones
  - Skull
  - Chin
  - Digits

Example:

- FL=flattened lamellae
- Mm=mesenchyme
- OB=osteoblasts
- BL=bone-lining cells
- CL=cement line (boundary line)
- 0=osteocytes
- V=blood vessels

Note: no cartilage cores

Bone is an early-maturing tissue, and is relatively resistant to nutritional or other restriction, therefore, body length (crown-rump) is often used as an indicator of fetal age.

Physical factors affecting bone

- Tissue interactions – fetal development of bone, muscle, tendons, etc. simultaneous;
- Tendons insert into developing cartilage model;
- Bone protuberances guided by insertions, forces acting upon bone;
  - e.g., tenotomy: muscle atrophies, bone continues to grow;
  - cartilage removal: muscles & tendons disappear
Effects of tension

1. The periosteum is attached to the bone (firmly) at the epiphyses and (loosely) at the diaphysis;
2. As the bone elongates, the periosteum is stretched, creating tension on the periosteum;

Post-natal growth

• Growth plate closure puts a stop to linear growth (depends upon age, species, breed, anatomical location);
• Crocodiles & alligators: GPs never close;
• No general rule (proximal vs. distal);
• No single event (GP closures occur over several years);
• Therefore, there are local regulators at each GP, although these are likely influenced by systemic factors and events (e.g. puberty).

Effects of tension

3. The periosteum responds to the increased tension by ↑ing its rate of cell proliferation;
4. This proceeds until it overshoots bone length, decreasing the tension on the bone;
5. The growth plate responds to the reduced tension by ↓ing its rate of proliferation and ossification, which elongates the bone and starts the entire cycle over again.

Post-natal growth

• First major regulator identified: growth hormone (1920’s-30’s)
• Hypophysectomy (hypox) – removal of anterior pituitary
  – No further bone elongation
  – Narrower GPs – no proliferative & hypertrophic zones
• GH replacement
  – GP widens, growth is near-normal

Effects of tension

• There is an optimal tension for bone growth and maintenance; this is related to the presence of an electrical current (e.g., fracture repair, electric blankets, high-voltage power lines)
• If periosteal attachments are severed, growth plate proliferation is very rapid;
• Similarly, if one GP is damaged or closes prematurely, the other GP may compensate by more rapid proliferation.

GH stimulates bone growth,

BUT: chondrocytes in vitro did not respond to GH

.: somatomedin hypothesis:

Anterior pituitary \( \rightarrow \) GH \( \rightarrow \) Liver \( \rightarrow \) IGF-I \( \rightarrow \) Growth plate
Evidence against the somatomedin hypothesis

- Infusion of GH into the growth plate of hypoxic rats increases GP width compared to the contralateral GP, ∴ the GH effect is also local
- Infusion of IGF-I is also effective
- GH is ineffective if IGF-I is blocked by a specific antibody
- Almost all tissues express mRNA for IGF-I (including chondrocytes)

Dual Effector Theory

- Circulating GH 'primes' the growth plate to respond to IGF-I
- Circulating GH also stimulates proliferative zone chondrocytes to produce IGF-I
- Locally–produced (paracrine) IGF-I stimulates chondrocyte proliferation and hypertrophy

Thyroid hormone

- Marked growth reduction in all hypothyroid animals
- Little data on direct effects in bone
- Increases width of growth plate (↑ recruitment of resting chondrocytes)

Abnormalities of GH function

- Giants:
  - excess GH prior to growth plate closure
  - wider proliferative zone
  - delayed GP closure
- Acromegaly:
  - excess GH after growth plate closure
  - growth by apposition only
  - affects mainly the cranium, digits, feet (disproportionate)
- Dwarfism:
  - several types, including
  - hypopituitary (low GH)
  - Laron (high GH but low IGF-I)
  - pygmies (normal GH and IGF-I, but tissues unresponsive)
  - hypothyroid

Single IGF1 Allele Is a Major Determinant of Small Size in Dogs

The domestic dog exhibits greater diversity in body size than any other terrestrial vertebrate. We used a strategy that vertebrate exploitation of the breed structure of dogs to investigate the genetic basis of size. First, through a genome-wide scan, we identified a major quantitative trait locus (QTL) on chromosome 15 influencing size variation within a single breed. Second, we examined genetic variation in the 15-megabase interval surrounding the QTL in small and giant breeds and found marked evidence for a selective sweep spanning a single gene (IGF1), encoding insulin-like growth factor 1. A single IGF1 single-nucleotide polymorphism haplotype is common to all small breeds and nearly absent from giant breeds, suggesting that the same causal sequence variant is a major contributor to body size in all small dogs.
**Glucocorticoids**

- **Direct effects:** ↓ chondrogenesis
- **Indirect effects:**
  - ↓ GH secretion by pituitary,
  - ↓ GP mRNA for GHR, GHBP, IGF-I, IGF-IR

**Sex steroids**

- **Pubertal growth spurt accounts for ~20% of adult height (growth spurt lasts ~ 22 months)**
- **Pubertal growth spurt due mainly to estrogen and testosterone (testosterone converted to estrogen)**

**Testosterone**

- **Stimulates GP cell proliferation (low doses)**
- **Enhances maturation of GP, accelerates closure (high doses)**
- **GH is required for its actions**
- **Acts mainly through conversion to estrogen**
  - Male ER(α) deficient mutant: no GP fusion, severe osteoporosis; not responsive to E therapy
  - Male CYP10 gene mutants: lack aromatase P450; similar effects, but are responsive to E

**Estrogen**

- **ERα and ERβ both present in GP**
- **Inhibit cartilage growth and enhance maturation of the GP;**
- **Low levels stimulate chondrocytes & osteoblasts indirectly (via ↑ IGF-I)**
- **High levels (e.g., at puberty) inhibit growth:**
  - ↓ cartilage growth; ↓ proliferative zone activity
  - ↑ maturation of the GP
- **Inhibit bone resorption by osteoclasts (thereby ↑ bone density)**

---

Growth factor | Osteoblast DNA | Collagen | Osteoclast resorption
--- | --- | --- | ---
Insulin-like growth factor-I (IGF-I) | + | + | -
IGF-II | + | + | 
Prostaglandins | + | + | +
Epidermal growth factor (EGF) | + | - | +
Transforming growth factor-α (TGF-α) | + | + | 
TGF-β1 | + | - | +
Platelet-derived growth factor (PDGF) | + | + | +
Fibroblast growth factor (FGFα, β) | ++ | - | 
Interleukin-1 (IL-1α, β) | + | + | +
Tumor necrosis factor (TNF) | - | - | -
Interferon-γ | - | - | -
Bone morphogenetic protein (BMP) | + | + | 

**Vitamin D (calcitriol)**
- Nutrient and hormone
- Helps to maintain normal plasma calcium
  - resorption of bone by osteoclasts
  - intestinal absorption of Ca and P
  - renal retention of PO4
- Direct effects on osteoblasts
  - collagen synthesis
  - osteocalcin synthesis
  - IGF-I synthesis
  -? osteoblast proliferation

**Regulation of calcium and phosphorus**
- All tissues/cells require precise concentrations of Ca²⁺ for proper function
- Circulating Ca²⁺ exchanges with tissue pools and the storage pool in bone
- 99% of body calcium (ca. 1 kg) is in the mineralized bone

**Calcitonin**
- Produced in the C cells of the thyroid gland
- Decreases bone resorption (direct effects on osteoclasts)

**Parathyroid hormone (PTH)**
- Principal role = maintenance of plasma calcium concentration
- Released by the parathyroid gland in response to low plasma [Ca²⁺]; undergoes further processing in the liver
- Raises plasma Ca²⁺ by stimulation of:
  - bone resorption by osteoclasts
  - renal tubule reabsorption of calcium
  - 1,25-(OH)₂D₃ production → increased intestinal Ca²⁺ absorption, bone resorption
- Lowers plasma P by stimulation of renal excretion, thus preventing harmful CaPO₄ precipitates in tissues
- PTH may be anabolic or catabolic, depending upon its interactions with other hormones and health/disease state