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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

Physiology, Bone

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Last Update: November 13, 2018.

Introduction

The adult human skeleton is composed of 206 bones. At birth, there are approximately 270 bones, with the final adult count decreasing as a portion of these bones fuse during phases of skeletal growth and maturiation. Bone is a metabolically active connective tissue that provides structural support, facilitates movement, and protects vital organs. It plays an important role in regulating mineral and acid-base balance homeostasis. It also provides the environment for hematopoiesis (blood cells production) within the bone marrow. Bone is composed of an extracellular matrix and bone cells (osteocytes). [0][0]

Function

Bone Cells

Bone cells make up about 10% of total bone volume. There are four types of cells:

1. Osteoprogenitor (Stem) Cells: Osteoprogenitor cells retain the ability to re-differentiate into osteoblasts. They reside in the bone canals, endosteum, periosteum, and marrow. They may regulate influx and efflux of mineral ions into and out of the bone extracellular matrix. They also are responsible for the formation of bone remodeling compartments (BRC) with a specialized microenvironment.
2. Osteoblasts - Bone Forming Cells: They are tightly packed on the surface of the bone. They synthesize and secrete bone matrix (osteoid). They also regulate bone mineralization by secreting alkaline phosphatase (a marker for bone formation) and a set of proteins: dentin matrix protein (DMP-1) and bone sialoprotein act as nucleators for mineralization. Osteocalcin, osteonectin are calcium and phosphate binding proteins, which regulate deposition of mineral by regulating the amount and of hydroxyapatite crystals. Osteoblasts have one of two fates: (1) remain quiescent osteoblasts lining cells or (2) become osteocytes. Osteoblasts regulate osteoclastogenesis (osteoclast formation) and osteoclastogenesis (osteocyte formation). Vitamin D and parathyroid hormone (PTH) stimulate osteoblasts to secrete macrophage CSF (M-CSF) and to express RANKL, which are important for osteoclastogenesis.
3. Osteocytes - Mechanosensing Cells: These account for 90% of all bone cells. They are derived from osteoblasts. They reside within a bone network called the lacuna canalicular system. They do not normally express alkaline phosphatase but do express osteocalcin and other bone matrix proteins. They maintain a connection with each other and bone surfaces via their cytoplasmic processes. Osteocytes are linked metabolically and electrically through gap junctions. Their primary function is mechanosensation. Osteocytes detect mechanical loading through physical deformation of bone matrix and fluid flow shear stress resulting from the flow of canalicular fluid through the lacuna canalicular network. Osteocytes act as orchestrators of bone remodeling, and they are also considered as endocrine cells. They secrete FGF23 to regulate serum phosphate level. FGF23 decreases renal and intestinal sodium and phosphate co-transporters expression and subsequently increases renal phosphate excretion by both kidneys.

4. Osteoclasts - Bone Resorbing Cells: These are multinucleated cells originated from mononuclear monocyte-macrophage cells. RANKL and macrophage CSF (M-CSF) are two cytokines that are critical for osteoclast formation. They are important for osteoclast precursors to proliferate and differentiate into mature osteoclasts. Osteoprotegerin (OPG) is a membrane-bound secreted protein that binds RANKL (see figure) to inhibit its action at the RANK receptor and subsequently inhibit osteoclastogenesis. Bone resorption depends on osteoclast secretion of hydrogen ions, tartrate-resistant acid phosphatase (TRAP) and cathepsin K enzymes. H+ ions acidify the resorption compartment beneath osteoclasts to dissolve the mineral component of the bone matrix, whereas cathepsin K and tartrate-resistant acid phosphatase (TRAP) digest the proteinaceous matrix, which is mostly composed of type I collagen. PTH stimulates osteoclast activity while calcitonin inhibits it.

Bone Extracellular Matrix

This makes up 90% of overall bone volume. It consists of inorganic (mineral) and organic matrices.

1. Inorganic Bone Matrix: accounts for 99% of the body storage of calcium, 85% of the phosphorus and 40-60% of the magnesium, and sodium. It is mainly in the form of hydroxyapatite [Ca10(PO4)6(OH)2] to provide the bone its strength, stiffness and the resistance to compressive forces.
2. Organic Bone Matrix: is secreted by osteoblasts and is predominantly type I collagen. It also contains glycoproteins, growth factors, and proteoglycans. Growth factors (such as osteocalcin, osteonectin, and bone sialoprotein) play important roles in osteoid formation, mineralization, and bone remodeling. Organic matrix gives bone its form and provides resistance to tensile forces.

Bone Remodeling

This is a physiological process in which old or damaged bone is removed by osteoclasts then replaced by new bone formed by osteoblasts. There is a tight coupling of bone formation to bone resorption to ensure no net change in bone mass or quality after each remodeling. It requires coordinated action of the four types of bone cells. The process involves four major distinct but overlapping phases:

- Phase 1: initiation/activation of bone remodeling at a specific site. The osteoclast precursors are recruited to BRC.
- Phase 2: bone resorption and concurrent recruitment of osteoprogenitors. Bone resorption represents the predominant event, but the recruitment of mesenchymal stem cells (MSCs) and/or osteoprogenitors into the BRC is also initiated.
- Phase 3: osteoblast differentiation and function (osteoid synthesis). Excavated bone is replaced with osteoid produced by osteoblasts.
- Phase 4: mineralization of osteoid and completion of bone remodeling. The osteoid is mineralized, and the bone remodeling cycle is concluded.

Clinical Significance

Osteoporosis [0][0][5][6][7][8]

This is a common disorder of bone remodeling which is characterized by low bone mass and structural deterioration of bone. It causes bone fragility and increased vulnerability to fractures. There are two types of osteoporosis:

Primary Osteoporosis:

Type I (Postmenopausal Osteoporosis)

- **Cause:** a decline in estrogen levels associated with menopause.

- **Pathophysiology:** estrogen deficiency causes an increase in osteoclast activity by increasing RANKL and M-CSF expression and inhibiting osteoclast apoptosis by reducing FasL expression by preosteoclasts.

Type II (Age-Related Osteoporosis or Senile Osteoporosis)

- **Cause:** age related and centered on osteoblasts (bone formation) [in addition to bone resorption in postmenopausal women].
- **Pathophysiology:** decreased bone formation in men and women is caused by changes in reactive oxygen species (ROS), insulin-like growth factor 1 (IGF-1) and PTH levels associated with aging.

Glucocorticoid - induced Osteoporosis (Secondary Osteoporosis)

- **Cause:** glucocorticoids are immunomodulatory drugs that are used to treat a variety of autoimmune disorders and inflammatory conditions such as rheumatoid arthritis and multiple sclerosis. Bone loss and increased risk of fractures are among common side effects of glucocorticoid treatment.
- **Pathophysiology:** glucocorticoids inhibit differentiation of osteoprogenitors into osteoblasts and promote their differentiation into adipocytes (fat cells). They also increase osteoblast apoptosis and impair their functions. Also, glucocorticoids target mature osteoclasts to prolong their life span which worsens the imbalance between bone formation and bone resorption in favor of bone resorption.

Questions

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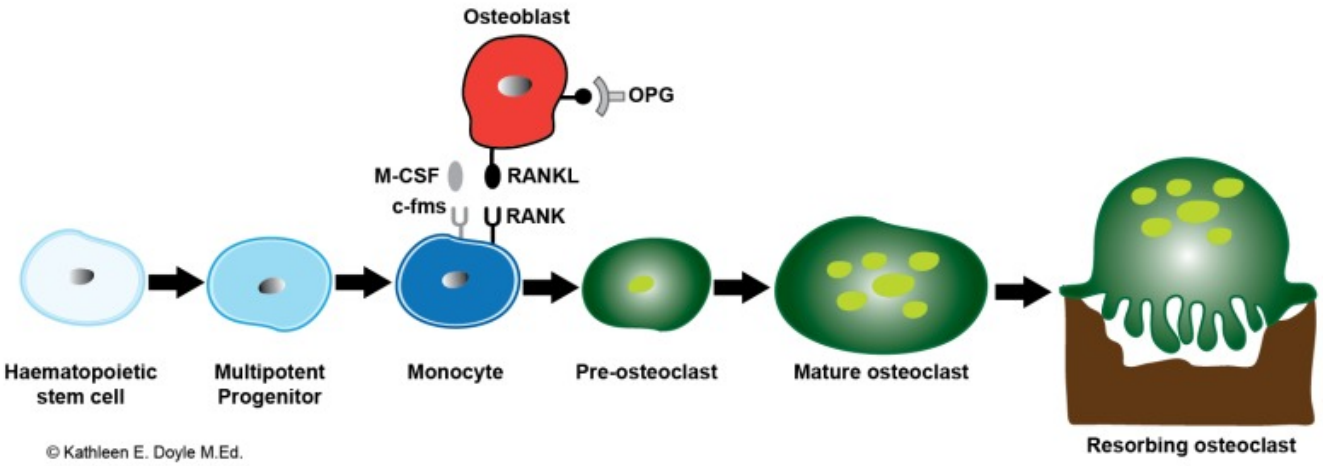
Figures



Schematic illustration of osteoclastogenesis. Bone-resorbing osteoclasts originate from hemopoietic cells of the monocyte–macrophage lineage under control of bone- forming osteoblasts. RANKL, the receptor activator of NF-κB ligand; M-CSF, macrophage colony stimulating factor; OPG, osteoprotegrin. Contributed by Kathleen E. Doyle M.Ed., Instructional Designer at the Oakland University William Beaumont School of Medicine.

Bookshelf ID: NBK441968 PMID: 28722997