Research Paper

Volume : 3 | Issue : 4 | April 2014 • ISSN No 2277 - 8179

Bone Remodeling: The Molecular Mechanism of Bone Physiology- A Review

Medical Science

KEYWORDS : Bone remodeling, Osteoblast, Osteoclast, RANK

Biplob Chowdhury Research Scholar, Dept. of Physical Education, Visva-Bharati.

ABSTRACT

Physiological bone remodeling is a highly coordinated process responsible for bone resorption and formation and is necessary to repair damaged bone and to maintain mineral homeostasis. In addition to the traditional bone cells (osteoclasts, osteoblasts, and osteocytes) that are necessary for bone remodeling, several immune cells have also been implicated in bone disease. This review discusses physiological bone remodeling, outlining the traditional bone biology in light of emerging data. Specifically discussed in detail are the cellular and molecular mechanisms of bone remodeling, including events that the five sequential phases of bone remodeling: activation, resorption, reversal, formation, and termination.

Introduction: Bone is a dynamic tissue that undergoes continual adaption during vertebrate life to attain and preserve skeletal size, shape, and structural integrity and to regulate mineral homeostasis. Bone modeling is responsible for growth and mechanically induced adaption of bone and requires that the processes of bone formation and bone removal (resorption), although globally coordinated, occur independently at distinct anatomical locations. Bone remodeling is responsible for removal and repair of damaged bone to maintain integrity of the adult skeleton and mineral homeostasis. This tightly coordinated event requires the synchronized activities of multiple cellular participants to ensure that bone resorption and formation occur sequentially at the same anatomical location to preserve bone mass.

Cells Involved in Bone Remodeling

Osteoclasts:

Osteoclasts are terminally differentiated myeloid cells that are uniquely adapted to remove mineralized bone matrix.[1] These cells have distinct morphological and phenotypic characteristics that are routinely used to identify them, including multi nuclearity and expression of tartrate-resistant acid phosphatase and the calcitonin receptor[2]. CSF-1 (colony- stimulating factor 1; also known as macrophage colony-stimulating factor) and RANKL (receptor activator of NF- B ligand) are critical cytokines required for survival, expansion, and differentiation of osteoclast precursor cells.[3] Osteoprotegerin (OPG)2 is a soluble decoy receptor for RANKL and a physiological negative regulator of osteoclastogenesis; loss of functional OPG in mice results in animals with osteoporosis (brittle bones) due to excessive osteoclastogenesis.[4]

Osteoblasts :

Osteoblasts are specialized bone-forming cells that express parathyroid hormone (PTH) receptors and have several important roles in bone remodeling: expression of osteoclastogenic factors, production of bone matrix proteins, and bone mineralization.[5] Osteoblasts develop from pluripotent mesenchymal stem cells that have the potential to differentiate into adipocytes, myocytes, chondrocytes, and osteoblasts under the direction of a defined suite of regulatory transcription factors.[6] The osteoblast resides along the bone surface at sites of active bone formation. They secrete type 1 collagen, the basic building block of bone; non-collagenous proteins including osteocalcin and alkaline phosphatase, which is essential for mineral deposition.[7] The principal function of the osteoblast is bone formation and these occur via two distinct mechanisms: the intramembranous ossification (flat bones of the skull and most of the clavicle) and the endochondral ossification, which produces most bones, involves the transformation of mesenchyme into a cartilage model that resembles the shape of the bone.[8] Approximately 50 to 70% of osteoblasts undergo apoptosis.[9]

Osteocytes:

Osteocytes are non-proliferative, terminally differentiated cells of the osteoblast lineage. They reside both in the mineralized bone matrix and in newly formed osteoid, locked inside small lacuna spaces in the hard substance of bone are smaller than osteoblasts and have lost many of their cytoplasmic organelles.[10-11] They compose over 90–95% of all bone cells in the adult skeleton and are thought to respond to mechanical strain to send signals of resorption or formation, due to their distribution throughout the bone matrix and extensive inter connectivity, osteocytes are thought to be one if not the major bone cell type responsible for sensing mechanical strain and orchestrating signals of resorption and formation. Evidence suggests that the primary function of the osteocyte relates to the determination and maintenance of bone structure. The osteocyte appears to be capable of relating the intensity of strain signals and the distribution of the strain throughout the whole bone into signals to regulate.[12] Microdamage in the bone matrix has been shown to initiate bone remodeling, the osteocytes located near these sites undergo apoptosis correlated with increased bone remodeling due to enhanced RANKL production and an increase in osteoclast formation, and the osteocytes may be the major source of RANKL during bone remodeling.[13-15] For some time it has been estimated that the average life of this cell would be 25 years. The percentage of dead osteocytes increases with age senescence, being from 1% to 75% rise in the eighth decade.[16]

Bone remodeling: The process

The normal bone remodeling is a process that couples bone resorption and bone formation, it occurs in discrete locations and involves a group of different kinds of cells and takes 2 to 5 years for an area on the bone surface to complete one bone remodeling cycle.[17]

The bone remodeling follows coordination of distinct and sequential phases of this process:

Activation Phase- The first stage of bone remodeling involves detection of an initiating remodeling signal, the activation is a continuing process that occurs at the cutting edge of the BMU, and this signal can take several forms as a direct mechanical strain on the bone that results in structural damage or hormone (e.g. estrogen or PTH) action on bone cells in response to more systemic changes in homeostasis.[17] Conceivably, osteocyte apoptosis and possible release of osteotropic growth factors and cytokines could be attractants for blood vessels, which would then subsequently initiate the formation of a resorptive of the bone remodeling compartment which are a prerequisite for osteogenesis, including bone development, fracture healing, and cortical bone remodeling that support recruitment of osteoblast progenitors to bone remodeling sites, thus highlight a link between activation of bone remodeling on the cancellous bone surfaces and activation of neighbouring bone marrow events.[18-20]

Resorption Phase- In this phase, the formation and activity of osteoclasts is controlled by cells of the osteoblast lineage that recruit osteoclast precursors to the remodeling site with the expression of the master osteoclastogenesis cytokines, CSF-1, RANKL, and OPG, is also modulated in response to PTH.[21,22]Remodeling is initiated by osteoclastic resorption, which erodes a resorption lacuna, they attach to the bone surface, sealing a resorbing compartment that they acidify by secreting H+ ions, facilitating dissolution of the bone mineral and thereby exposing the organic matrix to proteolytic enzymes that

degrade it, during resorption the bone matrix and bone mineral is digested. Some fragments can be used as biochemical markers for overall bone resorption.[23]

Reversal phase- In the reversal period the osteoclasts undergo apoptosis whilst osteoblasts are recruited and begin to differentiate, therefore the reversal phase is a transition from osteoclast to osteoblast activity. After withdrawal of the osteoclast from the resorption pit, bone-lining cells enter the lacuna and clean its bottom from bone matrix leftovers. This cleaning proves to be a prerequisite for the subsequent deposition of a first layer of proteins (collagenous) in the resorption pits and form a cement line (glycoprotein) that helps in attaching osteoblasts.[24]

Formation Phase- Collagen type I is the primary organic component of bone and accumulation contributes, in part, to the cessation of cell growth. When proliferation ceases, proteins associated with bone cell phenotype are detected, e.g. alkaline phosphatase enzyme, osteocalcin. Bone matrix is built up of type I collagen (88%) and the remaining 10% is composed of a large number of non-collagenous proteins (e.g. osteocalcin, osteonectin, bone sialoprotein and various proteoglycans) and lipids and glycosaminoglycans represent 1– 2%. For bone to assume its final form, hydroxylapatite is incorporated into this newly deposited osteoid. When an equal quantity of resorbed bone has been replaced, the remodeling cycle concludes.[25]

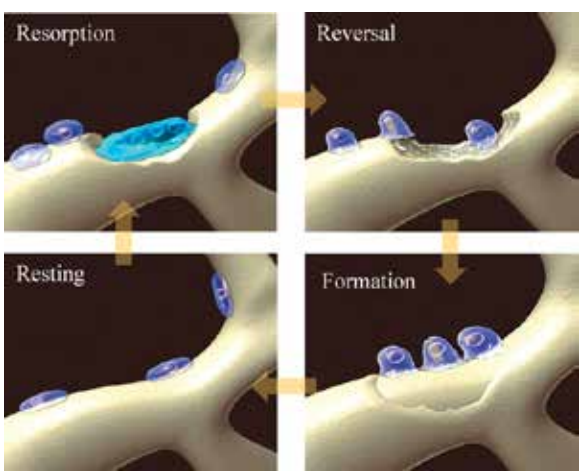

Figure 1. Remodeling cycle

Termination Phase- The termination signals are largely unknown, and include the terminal differentiation of the osteoblast. The cells then gradually flatten as they slow production, and finally they become quiescent lining cells. Some of the osteoblast differentiate into osteocytes and remain in the matrix. Bone remodeling is mediated by a balance of osteoblast and osteoclast cell activity, which together, maintain bone mass and mineral homeostasis. Both decreased bone formation and increased bone resorption may result in bone loss. Therefore, the stimulation of bone formation may be another important factor for the prevention and treatment of bone loss.

Conclusions: Bone is a specialized and dynamic tissue, in constant change. It has a complex structure and undergoes constant remodeling. The basic multicellular unit of bone, which comprises osteocytes, osteoclasts and osteoblasts, conducts the remodeling process. The current physiological bone-remodeling paradigm is incomplete, and deficiencies in understanding the mechanisms that couple bone resorption and formation are a barrier to successfully treating the numerous pathological bone diseases that result in bone loss.

REFERENCE

1. Bianco P, Gehron RP, Simmons PJ. (2008) Mesenchymal Stem Cells: Revisiting History, Concepts, and Assays. Cell Stem Cell. 2(4):313–319. | 2. Teitelbaum SL. (2000) Bone resorption by osteoclasts. Science. 289(5484):1504–1508. [23] Hill P. Bone remodelling. Br J Orthod. 1998;25:101–107. | 3. Yasuda H, Shima N, Nakagawa N, Yamaguchi K, Kinosaki M, Mochizuki SI, et al.(1998) Osteoclast differentiation factor is a ligand for osteoprotegeriny osteoclastogenesis inhibitory factor and is identical to RANCE/RANKL. Proc Natl Acad Sci U S A. 95(7):3597-3602. | 4. Hofbauer LC, Neubauer A, Heufelder AE. (2001) Receptor activator of nuclear factor-Kb ligand and osteoprotegerin: potential implications for the pathogenesis and treatment of malignant bone diseases. Cancer. 92(3):460–470. | 5. Li Z, Kong K, Qi W. (2006) Osteoclast and its roles in calcium metabolism and bone develop- ment and remodeling. Biochem Biophys Res Commun. 343:345–350. | 6. Carbonare LD, Innamorati G, Valenti M. (2012) Transcription Factor Runx2 and its Applica- tion to Bone Tissue Engineering. Stem Cell Rev and Rep. 8(3):891–897. | 7. Clarke B. (2008) Normal bone anatomy and physiology. Clin J Am Soc Nephrol. 3:S131– 139. | 8. Westendorf JJ, Kahler RA, Schroeder TM. (2004) Wnt signaling in osteoblasts and bone diseases. Gene. 341:19–39. | 9. Lynch MP, Capparelli C, Stein JL, Stein GS, Lian JB. (1998) Apoptosis during bone-like tissue development in vitro. J Cell Biochem. 68:31–49. | 10. Noble BS.(2008) The osteocyte lineage. B.S. Arch Biochem Biophys. 473:106–111. | 11. Bonewald LF. (2011) The Amazing Osteocyte. J Bone Miner Res. 26(2):229–238. | 12. Lanyon LE. Osteocytes, strain detection, bone modeling and remodeling. (1993) Calcif Tissue Int. 53:S102–S106; discussion S106-7. | 13. Nakashima T, Hayashi M, Fukunaga T, Kurata K, Oh-hora M, Feng JQ, et al.(2011) Evidence for osteocyte regulation of bone homeostasis through rankl expression. Nat Med. 17:1231–1234. | 14. O'Brien CA, Nakashima T, Takayanagi H. (2012) Osteocyte control of osteoclastogenesis. Bone. http://dx.doi.org/10.1016/j.bone.2012.08.121. | 15. Xiong J, Onal M, Jilka RL, Weinstein RS, Manolagas SC, O'Brien CA. (2012) Matrix-embedded cells control osteoclast formation. Nat Med. 17(10):1235–1241. | 16. Tate MK. (2003) Whither flows the fluid in bone? An osteocyte´s perspective. J Biomech. 36:1409-1424. | 17. Raggatt LJ, Partridge NC.(2010) Cellular and Molecular Mechanisms of Bone Remodeling. J Biol Chem. 285(33):25103–25108. | 18. Eriksen EF. (2010) Cellular mechanisms of bone remodeling. Rev Endocr Metab Disord. 11:219–227. | 19. Smit TH, Burger EH. (2000) Is BMU-Coupling a Strain-Regulated Phenomenon? A Finite Element Analysis. J Bone Miner Res. 15(2):301-307. | 20. Kristensen HB, Andersen TL, Marcussen N, Rolighed L, Delaisse JM. (2012) Increased presence of capillaries next to remodeling sites in adult human cancellous bone. J Bone Miner Res. 7(3): 589-94. | 21. Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, et al. (2009) TGF-β1-induced Migration of Bone Mesenchymal Stem Cells Couples Bone Resorption and Formation. Nat Med. 15(7):757–765. | 22. Teti A. Bone Development: Overview of Bone Cells and Signaling. Curr Osteoporos Rep. 9:264–273. | 23. Martin TJ, Sims NA. (2011) Osteoclast-derived activity in the coupling of bone formation to resorption. Trends Mol Med. 2005;11(2):76-81. | 24. Gallagher JC, Sai AJ. (2010) Molecular biology of bone remodeling: implications for new therapeutic targets for osteoporosis. Maturitas. 65(4):301–307. | 25. Confavreux CB. (2011) Bone: from a reservoir of minerals to a regulator of energy metabolism. Kidney Int Suppl. (121):S14-19. |