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# Bone Cell Function: A Review

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*Review Article*

# Bone Cell Function: A Review

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***Abstract***

Bone is dynamic tissue which is continuously formed and absorbed by its own cells in response to stimuli such as hormones, mechanical loading and growth factors. Understanding the function of bone cells is important, not only in orthopedic field but also in research study involving bone. Bone cells work in harmony to maintain a balance between bone formation and resorption, ultimately to control bone structure and function. Osteoblasts are cells, which contribute to deposition of organic components of bone extracellular matrix. They control recruitment, differentiation and maturation of osteoclasts that participate in resorption activity. In addition, osteoclasts associated with bone resorption also express several factors that regulate osteoblast function. Osteocytes, the terminally differentiated osteoblasts, act as the mechano-sensors and modulate both osteoblast and osteoclast activity, and regulate mineral homeostasis in bone tissue and mineral concentration in the blood. Similarly, bone lining cells are thought to play a role in regulation of calcium and phosphate metabolism in bone tissue, and aid osteoclasts and osteoblasts in bone remodeling.

**Keywords:** bone lining cells, cell interaction, osteoblasts, osteoclasts, osteocytes

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# บทคัดย่อ

## หน้าที่ของเซลล์กระดูก

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กระดูกเป็นเนื้อเยื่อที่มีการเปลี่ยนแปลงตลอดเวลา ทั้งในรูปแบบการสร้างใหม่และการสลายทดแทนกัน ซึ่งเป็นการตอบสนองต่อการกระตุ้นที่กระทำต่อเซลล์กระดูกเองได้แก่ ฮอร์โมน แรงที่มากระทำและปัจจัยที่ส่งผลต่อการเจริญเติบโต การทำความเข้าใจเกี่ยวกับหน้าที่ของเซลล์กระดูกมีความสำคัญ ไม่เพียงเกี่ยวข้องในเรื่องของงานทางออร์โธปิดิกส์ ยังรวมถึงงานวิจัยที่เกี่ยวข้องกับกระดูก โดยทั่วไปเซลล์กระดูกจะทำงานประสานกันเพื่อให้การสร้างและการสลายทดแทนกันเป็นไปอย่างสมดุล เซลล์ออสติโอบลาสต์ (osteoblast) ทำหน้าที่พาเอาแร่ธาตุเข้ามาเพื่อสร้างกระดูก และทำหน้าที่ควบคุม รวบรวม แยกแยะ การเจริญเติบโตของเซลล์ออสติโอคลาสต์ (osteoclast) ซึ่งเป็นเซลล์สลายกระดูก ขณะเดียวกันเซลล์ออสติโอคลาสต์หลั่งปัจจัยหลายอย่างที่ควบคุมเซลล์ออสติโอบลาสต์เช่นกัน ส่วนเซลล์ออสติโอไซต์เป็นเซลล์ที่เจริญต่อมาจากออสติโอบลาสต์ และเป็นเซลล์กระดูกที่เจริญเต็มที่แล้ว ทำหน้าที่เหมือนตัวรับแรงสัมผัส และปรับการทำงานของเซลล์ออสติโอบลาสต์และเซลล์ออสติโอคลาสต์ นอกจากนี้ยังทำหน้าที่ควบคุมสมดุลของแร่ธาตุในร่างกายและในกระแสเลือด เช่นเดียวกันกับเซลล์ bone lining ซึ่งมีส่วนสำคัญในการควบคุมเมตตาบอลิซึ่มของแคลเซี่ยมและฟอตเฟต และควบคุมเซลล์ออสติโอบลาสต์และเซลล์ออสติโอคลาสต์ในการสร้างและสลายของกระดูก

คำสำคัญ: bone lining cell เซลล์ออสติโอบลาสต์ เซลล์ออสติโอคลาสต์ เซลล์ออสติโอไซต์

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## *Introduction*

Bone has a number of functions including protection, movement, leverage, mineral storage, and a source of hematopoietic cells and stem cells (Boyce and Xing, 2007). Bone metabolism is dynamic with continuous bone formation and resorption (Kwan Tat et al., 2004). A balance of these two opposing activities guarantees microstructure and function of the bone. Osteoblasts secrete bone extracellular matrix which is subsequently mineralized to build strength and hardness. In contrast, osteoclasts produce acids and enzymes to destroy the bone matrix and the structure of bone tissue (Nakamura, 2007). Although they act in two opposing directions, these two cell types interact to harmonize and modulate bone remodeling. Osteoblasts express several factors to regulate the differentiation and activity of osteoclasts (Phan et al., 2004). Conversely, osteoclasts also exert modulatory signals to control osteoblastogenesis (Karsdal and Henriksen, 2007). Moreover, these two cell types are ruled by osteocytes whose additional function is to maintain mineral equilibrium and to target distant organs such as kidney to adjust mineral excretion (Bonewald, 2011). Bone remodeling may also be aided by bone lining cells (Kim et al., 2012) which were thought to make a negligible contribution to the process (Nakamura, 2007). This review describes the functions of bone cells, the interaction between osteoblasts and osteoclasts, and the control mechanisms asserted by osteocytes.

### *Osteoblasts Form Bone Matrix and Control Osteoclast Activity*

Osteoblasts originate from multi-potential mesenchymal progenitors (Martin et al., 2011) and in metabolical active stage, osteoblasts are cuboidal and basophilic. However, they are flattened and less basophilic when resting (Samuelson, 2007). Their nuclei are located at the end of the cells where they are in contact with capillaries. Productive life of a lamellar osteoblast in human is about 3 months. Being specialized stromal cells, osteoblasts are exclusively responsible for the formation, deposition and mineralization of bone tissue (Phan et al., 2004). These cells secrete osteoid, the organic components of bone matrix, consisting of collagen and non-collagenous proteins such as glycoproteins and proteoglycans (Jubb et al., 2007). The organic bone matrix is subsequently mineralized by the deposition of calcium phosphate crystals and hydroxyapatite to create hardness and strength of the bone. Osteoblasts also produce several bone morphogenetic proteins (BMPs) and growth factors such as insulin-like growth factor (IGF), transforming growth factor-β (TGF-β), which are stored in the mineralized bone matrix (Nakamura, 2007). The fact that matrix metalloprotease-13 (MMP-13) is secreted by osteoblasts under regulation of parathyroid hormone suggests that these cells may also participate in degradation of collagen during bone resorption in

concert with osteoclasts (Nakamura, 2004; Nakamura et al., 2007).

Osteoblasts also regulate differentiation and the bone resorption activity of osteoclasts. Osteoblasts produce macrophage-colony stimulating factor (M-CSF) that is indispensable for both proliferation of osteoclast progenitors and their differentiation into mature osteoclasts, enhancing osteoclastogenesis. Lacking M-CSF, mice have very few osteoclasts and develop osteopetrosis. The effect of M-CSF on osteoclasts seems to be phasic, since it is reported that M-CSF has negligible effect on the formation of osteoclasts and activity of mature osteoclasts, but it does influence the number of osteoclast progenitors. The secretion of M-CSF is up-regulated by the binding of parathyroid hormone to its receptor on the surface of osteoblasts.

Discovery of osteoprotegerin (OPG), a receptor activator of nuclear factor kappa-B ligand (RANKL) which is derived from osteoblasts, leads to further understanding of the mechanism of the cross-communication between osteoblasts and osteoclasts (Boyle et al., 2003). RANKL is a trans-membrane protein on the surface of osteoblastic cells that binds to its own receptor, RANK, which is on the surface of both osteoclast progenitors and mature osteoclasts (Hsu et al., 1999). By expressing RANKL, osteoblasts can promote the formation of osteoclasts (Boyce and Xing, 2007). The expression of RANKL is induced by bone resorption stimulating factors such as $1,25(OH)_2D_3$, prostaglandin E2 (Singh et al., 2012), parathyroid hormone (Huang et al., 2004), and interleukin-1 (Nakamura, 2007). On the other hand, it can be down-regulated by estrogen (Srivastava et al., 2001). In contrast to the effect of RANKL, OPG protects the skeleton from excessive resorption by binding to RANKL, and thereby preventing it from binding to its receptor, RANK (Boyce and Xing, 2007). Collectively, the RANK/RANKL/OPG axis has a pivotal role in the control of osteoclastogenesis in which the RANKL/OPG ratio is an indispensable determinant of the formation of osteoclasts and bone resorption activity. The expression of OPG is up-regulated by estrogen, TGF-β and BMPs (Nakamura, 2007) and down-regulated by 1, $25(OH)_2D_3$ (Horwood et al., 1998), while the osteoclast expression of RANK is induced by low intensity laser irradiation (Aihara et al., 2006).

Osteoblasts may control the osteoclast formation by other mechanisms. M-CSF expressed by osteoblasts binds to c-Fms receptors on the osteoclast surfaces (Suda et al., 1999). Interestingly, osteoblasts also produce interleukin-34 (IL-34), which is a ligand for c-Fms receptor (Lin et al., 2008). Similar to M-CSF, IL-34 promotes macrophage colony formation, but in a different way (Chihara et al., 2010). This cytokine is believed to involve in the differentiation of hematopoietic progenitor cells into quiescent osteoclast progenitors, which subsequently circulate to find bone and finally differentiate into osteoclasts (Yamashita et al., 2012). Osteoblasts can also secrete and express several other cytokines such as IL-1α (Lomri et al., 2001), IL-6, IL-8, IL-10 (Hyzy et al., 2012), IL-11 (Sakai et al., 1999), and tumor necrosis factor alpha (TNF-α). Almost all of these factors promote osteoclastogenesis, and all these mechanisms are RANKL-independent (Bendre et al., 2003; Kudo et al., 2003), except IL-10, which inhibits the generation of osteoclasts (Evans and Fox, 2007). A series of bone morphogenetic proteins, i.e BMP2-9,15, are derived from osteoblasts as well (Suttapreyasri et al., 2006). BMP2, 4, 5, 6 are capable of promoting osteoclastic bone resorption (Kaneko et al., 2000; Wutzl et al., 2006), whereas BMP7 inhibits osteoclast generation (Maurer et al., 2012). Recently, a protein named Wnt5a expressed by osteoblasts has been found to promote the expression of RANK in osteoclast precursors, thereby enhancing osteoclastogenesis (Maeda et al., 2012). By contrast, another product of osteoblasts, semaphorin-3A, is reported to suppress osteoclast differentiation by binding to neuropilin-1 receptor and subsequently inhibiting the effect of RANKL (Hayashi et al., 2012). Thus, findings show that osteoblasts express several signals to control the formation of osteoclasts and the bone resorption activity.

***Osteoclasts Not Only Absorb Bone, But Also Control Osteoblast Activity***

Osteoclasts are giant cells with acidophilic cytoplasma and 2 to 100 nuclei. It was thought that osteoclasts were the result of the fusion of osteoblasts as they can dissociate again into osteogenic precursors. However, it is now widely accepted that osteoclasts are derived from myeloid progenitors of the monocyte-macrophage lineage. Osteoclasts have a unique ultrastructure called "ruffled border", which is a complex interfolded finger-like structure that helps the cells in move during their bone resorption activity. Adjacent to and surrounding the "ruffled border" is the "sealing zone", where the plasma membrane of the osteoclasts comes very close to the bone surface to ensure attachment (Martin et al., 2011). The life expectancy of human osteoclasts is dependent of the location and need, and varies from about 10 days to 6 weeks.

Osteoclasts are responsible for the bone resorption, and the differentiation and activity of osteoclasts are regulated by the expression of several factors by other bone cells. After being recruited, differentiated and mature, osteoclasts attach to the bone surface, and secrete lactic and citric acids to lower the pH and facilitate the dissolution of minerals in the bone matrix (Samuelson, 2007). The digestion of organic components of the bone matrix is conducted by lysosomal enzymes, i.e. cathepsin K and matrix metallopeptidase-9, which are in charge of degradation of collagen and gelatin, respectively (Nakamura, 2007). The inactivation of osteoclasts is attributed to calcitonin, a thyroid hormone which causes a decrease in the number of nuclei per osteoclast, the number of osteoclasts and the number of osteoclast progenitors (Jubb et al., 2007). This hormone also causes the destruction of actin filaments, the loss of clear zone, and the retraction of osteoblasts, and subsequent detachment of osteoclasts from the bone surface (Nakamura, 2007).

In addition to functioning as bone absorbing cells, osteoclasts are also involved in the control of osteoblast activity. One reported that osteoclasts synthesize and secrete hepatocyte growth factor (HGF), which supports osteoblasts entering their cell cycle and stimulates DNA synthesis in osteoblasts. This growth factor also enhances osteoblast differentiation on the hydroxyapatite surface (Hossain et al., 2005). However, HGF is also expressed by osteoblasts (Taichman et al., 2001). Therefore, the effect of HGF, which is expressed by osteoclasts, on the osteoblasts. Phan et al. (2004), who suggested that HGF secreted by surrounding osteoblasts might be as important as osteoclasts.

Sclerostin produced by mouse osteoclasts is also reported to negatively regulate the bone formation by repressing the differentiation and/or function of osteoblasts (Kusu et al., 2003). Recently, Ota et al. (2012) also suggested that murine osteoclasts expressed sclerostin in quantities that may impair the bone formation in an age-dependent manner. Interestingly, the expression of sclerostin by osteoclasts in 24-month-old mice is significantly elevated in conditioned media than that by osteoclasts from 6-week-old mice. In human, by contrast, osteoclasts do not produce sclerostin (Winkler et al., 2003), and that information in other species is yet to be identified. Therefore, the effect of osteoclasts on osteoblasts via osteoclast-derived sclerostin needs further examination, and the age of animals should be taken into consideration.

Karsdal et al. (2008) suggested that osteoclasts secreted signals that induce bone formation. They collected conditioned media from human osteoclasts cultured on bone and plastic to test their effects on bone nodule formation by osteoblasts. The results showed that both conditioned media promoted bone formation, whereas the non-conditioned medium did not. More evidence concerning the interaction between osteoblasts and osteoclasts is now available since Zhao et al. 2006 reported that the molecule ephrin B2 present on the surface of osteoclasts expressed anabolic signals to the osteoblasts by binding to corresponding EphB4 receptors on the osteoblasts. The binding of ephrin B2 to EphB4 not only enhances bone formation, but also inhibits bone resorption (Zhao et al., 2006). By contrast, platelet derived growth factor-BB (PDGF-BB) produced by osteoclasts inhibits osteoblastogenesis (Kubota et al., 2002). This mechanism was elucidated by a discovery that PDGF-BB binds to PDGF-BB-β receptor on the surface of osteoblasts (Sanchez-Fernandez et al., 2008). In addition, osteoclasts positively modulate the osteoblast activity by producing BMP6, Wnt10b and sphingosine kinase-1 (Pederson et al., 2008).

**Osteocyte Regulates Bone Remodeling and Mineral Homeostasis**

Approximately 10-20% of osteoblasts are enclosed in the bone matrix, and become osteocytes (Franz-Odendaal et al., 2006). During this transformation time, there is substantial change in cell morphology. Nascent and mature osteocytes are about 30% and 70% volumetrically smaller than osteoblasts, respectively (Knothe Tate et al., 2004). Nascent osteocytes develop processes toward mineralization and subsequently towards vascularity when they are mature (Hekimsoy, 2008). Osteocytes are considered to be terminally differentiated and the most abundant cells in bone tissues. They have extremely large surface areas because of numerous cytoplasmic processes (Nakamura, 2007). Osteocytes of mature lamellar bone are flat or plump oval cells with more branching processes than those of woven bone. The life cycle of osteocytes can be up to 35 years in humans and many years in other animals (Jubb et al., 1993). The death of osteocytes is considered the consequence of senescence, degeneration, necrosis, apoptosis and/or osteoclastic engulfment (Knothe Tate et al., 2004).

Being the most abundant cells in bone tissues, osteocytes express various functions such as mechano-sensor, regulation of mineral metabolism, remodeling of perilacunar matrix and regulation of bone resorption and formation. The change in mechanical loading and PTH may result in the alteration of osteocyte activity, and modulation of bone resorption and formation. It is suggested that the mechanical loading imposes the interstitial fluid flow, which may deform osteocytes, their processes and cilia, and subsequently causes changes in cells activity (Hekimsoy, 2008). Consistently, Bonewald. (2006) proposed that osteocytes might sense the load through cell body processes and celia. Mechanical loading stimulates dentin matrix protein 1 (DMP1) expression in osteocytes *in vivo*, resulting in alteration of the osteocyte matrix microenvironment by inducing formation of osteopontin, bone sialoprotein, etc. (Gluhak-Heinrich et al., 2003). Moreover, loading causes the release of nitric oxide, ATP, prostaglandin E2, and promotion of dendritic elongation (Bonewald, 2011). Furthermore, unloading up-regulates the expression of sclerostin from osteocytes (Kogianni et al., 2008), whereas PTH down-regulates (O'Brien et al., 2008). Similarly, osteocyte gene expression of *Sost*, which encodes sclerostin, is changed due to the change of mechanical loading (Robling et al., 2008).

Osteocytes may regulate phosphate homeostasis and mineralization. The mechanism in which osteocytes modulate mineral homeostasis is thought to be conducted through expressing their molecular products such as DMP1, fibroblast growth factor-23 (FGF-23), phosphate regulating neutral endopeptidase on chromosome X (PHEX) and matrix extracellular phosphoglycoprotein (MEPE) (Bonewald, 2007; Gluhak-Heinrich et al., 2007). DMP1 is pivotal for the normal osteocyte activity and mineralization since the absence of this protein causes defective osteocyte maturation and increased FGF-23 expression, leading to excessive excretion of phosphate in the kidney. In human and many animal species, rickets and osteomalacia, which are typically featured with soft bone and defective mineralization, are widely known as the cause of vitamin D deficiency (Dittmer and Thompson, 2011). In mice, these diseases are found in individuals who lack DMP1 (Feng et al., 2006). Increases in MEPE

expression result in the degradation of bone extracellular matrix and hypophosphatemia, which is due to phosphaturia (David et al., 2010). PHEX deficiency is necessary for the expression of FGF-23 and MEPE (Liu, 2006; David, 2009). In addition, healthy osteocytes are responsible for removal and replacement of the perilacunar matrix and potentially play a role in mineral homeostasis (Bonewald, 2011). Based on these observations, Bonewald (2011) proposed that the osteocyte network functioned as an endocrine system that acted beyond the bone tissues, targeting distant organs such as kidney.

Osteocytes can modulate both bone resorption and formation through their effects on osteoblasts and osteoclasts. Conditioned medium (CM) from osteocytes stimulates the proliferation of bone marrow stem cells and their differentiation into osteoblasts (Heino et al., 2004). Under physical contact, which is a prerequisite, osteocytes exposed to this fluid shear rapidly increase alkaline phosphatase activity of osteoblasts (Taylor et al., 2007). Furthermore, osteocytes produce low-density lipoprotein receptor related protein-5 (LRP-5) and LRP-6 in which the former protein promotes increased bone mass by enhancing osteoblast differentiation (Cui et al., 2011). In contrast, the latter protein inhibits RANKL expression, resulting in decreased osteoclastogenesis and bone resorption (Kubota et al., 2008). It is hypothesized that the expression of LRP-5 is inversely mediated by hormone serotonin since patients with a high bone mass phenotype due to the activation of a LRP-5 gene mutation have low plasma serotonin levels (Frost et al., 2010). By contrast, PTH signaling up-regulates the LRP-5 expression in osteocytes, and thereby increasing the osteoblast number and bone mass (O'Brien et al., 2008).

Osteocytes support the formation and activation of osteoclasts through the expression of large amounts of M-CSF and RANKL. Moreover, the RANKL/OPG ratio expressed by osteocytes is greater than those by osteoblasts and stromal cells (Zhao et al., 2002). On the other hand, osteocytes also produce TGF-β to inhibit osteoclastic bone resorption, and the expression of TGF-β is elevated if the osteocytes are treated with estradiol 17-β (Heino et al., 2002).

Osteocytes also modulate bone remodeling through expression of osteoprotegerin (OPG) and sclerostin. OPG expression in osteocytes is stimulated by mechanical loading (Terai et al., 1999). Down-regulation of OPG is in parallel with the depletion of Wnt/β-catein in osteocytes, and thereby predisposing individuals to porous bone (Kramer et al., 2010). In contrast to OPG, which inhibits bone resorption, sclerostin produced by osteocytes inhibits bone formation (Poole et al., 2005). It is believed that sclerostin reduces the lifespan of osteoblasts by stimulating apoptosis (Sutherland et al., 2004). The effect of sclerostin on bone resorption is controversial. Li et al. (2008) reported that sclerostin had no effect on bone resorption. However, recently it has been denoted that sclerostin also promotes osteoclast formation (Wijenayaka et al., 2011). Its expression by osteocytes is reduced by mechanical stimulation (Robling et al., 2008) and parathyroid hormone (Bellido et al., 2005), and is stimulated by calcitonin (Gooi et al., 2010). In addition, sclerostin and Dickkopf-related protein-1 (Dkk1), which is also expressed by osteocytes, are two negative regulators of Wnt/β-catein pathway (Bonewald, 2011).

Apoptotic osteocytes express apoptotic bodies that are responsible for initiating the osteoclastic bone resorption on quiescent bone surfaces. Unlike the case of healthy osteocytes, the mechanism in which the apoptotic osteocytes increase osteoclastogenesis is independent of the RANK/RANKL/OPG axis because the addition of OPG does not influence the osteoclastogeneic activity of apoptotic osteocytes (Kogianni et al., 2008).

***Bone Lining Cells Aid Osteoclasts and Osteoblasts in Bone Remodeling***

Bone lining cells (BLCs) are flattened in shape, with few cell organelles. With this morphological feature, BLCs are believed to have little or no involvement in bone formation (Nakamura, 2007). However, these cells are found to contribute to the bone remodeling, and to affect the concentration of minerals in blood and bone tissues. It is observed that mechanical loading stimulates bone formation by reactivation of BLCs to become active osteoblasts. Similarly, BLCs can be reactivated by intermittent treatment of parathyroid hormone (PTH) (Kim et al., 2012). The increase in bone formation with PTH treatment is not associated with cell proliferation, but most likely due to activation of preexisting quiescent BLCs to osteoblasts. PTH and calcitonin directly target BLCs, influencing Ca : $PO_4$ ratios in mitochondria, suggesting that these two hormones act on BLCs to modulate mineral concentrations of blood and temporary storage of calcium at bone surfaces.

These cells are believed to participate in the bone resorption activity, thereby being partly responsible for the bone remodeling. Before the osteoclastic activity, BLCs digest non-mineralized collagen protruding from bone surfaces. Moreover, bone resorption by osteoclasts is not completed, and these cells leave remnants of demineralized non-digested bone collagens behind after their withdrawal. In their turn, BLCs digest collagens left by osteoclasts in the resorption lacunae. Interestingly, they further form a cement line and deposit a thin layer of fibrillar collagen on the cleaned bone surfaces that may facilitate the subsequent osteoblast activity (Everts et al., 2002).

## *Conclusions*

Mutual interaction among bone cells is strongly evident from this review. Osteoblasts control the differentiation and bone resorption activity of osteoclasts via several mechanisms in which RANK\RANKL\OPG axis is prevalent and dominant. In addition, many other factors such as M-CSF, Wnt5a, semaphorin 3A, ILs and BMPs also express their effects on osteoclasts either directly or indirectly. The expressions of ephrin B2 and PDGF-BB in osteoclasts, and the discovery of EphB4 and PDGF-

BB receptors in osteoblasts are undeniable evidence which proves that osteoclasts express signals to regulate the osteoblastogenesis and bone formation. In response to mechanical loading, PTH, 1, 25$(OH)_2D_3$ and estrogen, osteocytes produce several factors to modulate bone formation and resorption, mineralization of the bone matrix, and mineral homeostasis in bone tissues. Bone lining cells aid both osteoclasts and osteoblasts in bone remodeling by absorbing remnants left by osteoclasts in the bone lacunae and secreting cement lines and fibrillar collagens to facilitate osteoblasts deposition and bone formation. Though various findings have partly explained the communication among bone cells, other mechanisms are believed to exist and in need of elucidation. Collectively, bone cells work in harmony, and mutually interact to ensure the balance between bone formation and bone resorption.

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