Advances in Research on Aberrant Bone Formation in Osteoporosis Treatment: Postprint

Authors: Yang Yang, Gao Xi, Gao Xi

Date: 2025-05-29T00:00:00+00:00

Abstract

Osteoporosis is a clinically common skeletal disease triggered by multiple factors. Its primary mechanism involves altering the inflammatory microenvironment of the body, promoting increased osteoclastogenesis, which subsequently leads to enhanced bone resorption and decreased bone mass. Paradoxical bone formation, conversely, is a process that regulates bone formation and increases bone mass by modulating apoptosis of a subset of osteoblasts, thereby influencing macrophage efferocytosis to promote osteoblast differentiation. Osteoblasts primarily participate in bone formation, while osteoclasts are involved in bone resorption; together, they mediate the regulation of bone homeostasis. Under normal homeostatic conditions, approximately 50% of osteoblasts in the bone remodeling site undergo apoptosis. When apoptosis of a subset of osteoblasts triggers paradoxical bone formation, macrophages are recruited and perform efferocytosis. Under the influence of efferocytosis, macrophages polarize into the M2 phenotype. M2 macrophages regulate osteoblast differentiation and inhibit osteoclastogenesis, thereby exerting an inhibitory effect on bone resorption while simultaneously enabling fresh osteoblasts to rapidly occupy the positions of original senescent osteoblasts to continue participating in bone formation. Since fresh osteoblasts produce a greater amount of bone formation than senescent osteoblasts, bone mass becomes significantly increased compared to that before apoptosis. Promoting apoptosis of a subset of osteoblasts in organisms with osteoporosis may reverse the condition by increasing bone mass, suggesting that paradoxical bone formation holds promise as a novel therapeutic direction for osteoporosis. Therefore, this article proposes treating osteoporosis through “paradoxical bone formation” and analyzes its underlying mechanisms, aiming to provide new insights for osteoporosis-related research and therapy.

Full Text

Preamble

Research Progress of Paradoxical Bone Formation in Osteoporosis Treatment

YANG Yang[1], GAO Xi[2]*

[1]The First Clinical Medical College, Heilongjiang University of Chinese Medicine, Harbin 150040, China
[2]The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin 150040, China

*Corresponding author: GAO Xi, Chief physician/Doctoral supervisor; E-mail: gaoxi2025@163.com

Abstract
Osteoporosis is a common clinical skeletal disease caused by multiple factors. Its primary mechanism involves altering the body' s inflammatory microenvironment, which promotes increased osteoclast generation and subsequently enhances bone resorption while reducing bone mass. Paradoxical bone formation, conversely, is a process that regulates bone formation and increases bone mass by modulating apoptosis in a subset of osteoblasts, thereby influencing macrophage efferocytosis to promote osteoblast differentiation. Osteoblasts primarily participate in bone formation, while osteoclasts mediate bone resorption; together, they regulate bone homeostasis. Under normal homeostatic conditions, approximately 50% of osteoblasts in remodeling bone undergo apoptosis. When partial osteoblast apoptosis triggers paradoxical bone formation, macrophages are recruited to perform efferocytosis, which polarizes them toward the M2 phenotype. M2 macrophages regulate osteoblast differentiation and inhibit osteoclast generation, suppressing bone resorption while enabling fresh osteoblasts to rapidly occupy the positions vacated by senescent osteoblasts and continue participating in bone formation. Since fresh osteoblasts produce more bone than their senescent counterparts, bone mass increases significantly compared to pre-apoptosis levels. Promoting apoptosis in a subset of osteoblasts in osteoporotic individuals may therefore reverse bone loss, suggesting that paradoxical bone formation could represent a novel therapeutic direction for osteoporosis. This paper proposes treating osteoporosis through "paradoxical bone formation" and analyzes its underlying mechanisms to provide new insights for osteoporosis research and clinical treatment.

Keywords
Osteoporosis; Paradoxical bone formation; Osteoblast apoptosis; Macrophage; Efferocytosis

Funding
Heilongjiang Provincial Natural Science Foundation Project (LH2021H092); Heilongjiang Provincial Special Project for Research on Popularization of Tradi-

tional Chinese Medicine Classics (ZYW2023-046)

Citation
YANG Y, GAO X. Research progress of paradoxical bone formation in osteoporosis [J]. Chinese General Practice, 2025. DOI: 10.12114/j.issn.1007-9572.2024.0675. [Epub ahead of print]

1 Overview of Paradoxical Bone Formation

Paradoxical bone formation is a process that regulates bone formation and increases bone mass by modulating apoptosis in a subset of osteoblasts (OBs), thereby influencing macrophage (Mø) efferocytosis and promoting differentiation of fresh osteoblasts. Historically, osteoblast apoptosis was considered detrimental to bone homeostasis. However, recent research has revealed that approximately 50% of osteoblasts undergo apoptosis at bone remodeling sites under steady-state conditions, suggesting that osteoblast apoptosis may represent an important mechanism for promoting bone formation. This has become a hot topic in recent years, with studies exploring the treatment of osteoporosis through regulated programmed cell death in osteoblasts [9-10]. Based on this phenomenon, Batoon et al. [8] conducted pro-apoptotic experiments on less than 50% of osteoblasts and observed increased bone mass in mouse vertebrae. These experiments also demonstrated increased macrophages on bone surfaces and elevated bone marrow-derived mesenchymal stem cells (BMSCs), with a positive correlation between macrophage and BMSC numbers, while osteoclast counts remained unaffected. This phenomenon, contrary to the widely accepted theory that inhibiting osteoblast apoptosis promotes bone formation, was termed "paradoxical bone formation" [8].

Since osteoblast bone-forming capacity gradually declines with age, senescent osteoblasts produce less bone than their fresh counterparts [11-12]. Inducing apoptosis in senescent osteoblasts not only promotes BMSC differentiation into osteoblasts but also allows fresh osteoblasts to replace senescent ones, ultimately increasing bone mass. Based on this theory, paradoxical bone formation may represent a promising new approach for osteoporosis treatment.

2 Paradoxical Bone Formation and Bone Homeostasis

Bone is a dynamic tissue composed of osteocytes, osteoblasts, osteoclasts, and other elements. Throughout life, bone exists in a constant state of "use it or lose it" remodeling to adapt to biomechanical changes. This remodeling process consists of two major phases: bone resorption and bone formation, with the balance depending on the dynamic equilibrium between osteoblasts and osteoclasts. The interplay between osteoblast-mediated bone formation and osteoclast-mediated bone resorption is exquisitely regulated, with osteocytes serving as crucial mediators of communication between these cell types [13-14]. This crosstalk is es-

sential for maintaining bone mass [15]. Postnatal bone homeostasis is regulated by multiple mechanisms acting primarily on osteoblasts and osteoclasts, as well as through bone immunology. Paradoxical bone formation is intimately linked to both osteoblast-mediated bone formation and osteoclast-mediated bone resorption, while also being regulated by macrophages in the context of bone immunology.

2.1 Paradoxical Bone Formation and Osteoblasts

Osteoblasts are key cells involved in bone formation, differentiating from bone marrow-derived mesenchymal stem cells (BMSCs) [16-17], which represent important regulators of postnatal bone homeostasis and can be considered osteoblast progenitor cells. Promoting bone formation can thus be achieved by modulating BMSC differentiation into osteoblasts [18]. This differentiation process is complex and closely associated with the STAT3 signaling pathway, Runx2, Smad proteins, BMP-2, the transforming growth factor-β (TGF-β) superfamily, and the Wnt signaling pathway. STAT3 activation initiates transcription [19], representing the first step in BMSC differentiation. Runx2 possesses the ability to inhibit differentiation of BMSCs into other lineages, directing them specifically toward the osteoblast fate, while BMP-2 and Wnt signaling pathways enhance Runx2 expression. The combined action of these mechanisms ultimately promotes osteoblast differentiation [20].

When the STAT3 pathway is activated in BMSCs, downstream factors such as Runx2 are triggered, leading to activation of Smad effectors and Smad-independent pathways like the p38 mitogen-activated protein kinase (MAPK) pathway. This enhances TGF-β/BMP-related signal transduction, promoting expression of the osteoblast-specific transcription factor Osterix, activating protein kinase B (Akt), and regulating the Wnt pathway. The canonical Wnt pathway collaborates with Runx2 and Osterix to promote osteoblast differentiation and maturation, while also exerting complex stimulatory and inhibitory effects on TGF-β activity. Akt further enhances expression of Runx2-positive cells, providing positive regulation of osteoblast differentiation and maturation [19,21-31]. Additionally, BMP-2 activation is influenced by parathyroid hormone (PTH), which activates downstream effector proteins to stimulate BMP-2 expression, promoting osteoblast activity while inhibiting apoptosis [32].

Research has also shown that BMP signaling is affected by Hedgehog (Hh) pathways, which have five signaling factors that receive BMP signals and upregulate PTH expression. Sonic hedgehog (Shh) cooperates with BMP-2 in osteoblast differentiation and upregulates Osterix expression, while Indian hedgehog (Ihh) acts directly on BMSCs to promote osteoblast differentiation and interacts with the Runx2/Smad pathway [33]. Notch signaling pathways also play important roles in postnatal bone homeostasis and osteoblast differentiation, promoting expansion of immature osteoblasts [34-35]. Insulin-like growth factor (IGF) further promotes BMSC-to-osteoblast differentiation through interactions with Wnt, BMP, TGF-β, and Hh/PTH signaling pathways [36].

The mechanisms underlying BMSC differentiation into osteoblasts are illustrated in Figure 1 [Figure 1: see original paper].

Although paradoxical bone formation differs from traditional theories that promote bone formation by directly stimulating osteoblast differentiation, it ultimately influences osteoblast differentiation and bone formation regulation through effects on BMSCs and expression of related pathways and factors. Paradoxical bone formation also occurs in normal bone homeostasis, where approximately 50% of osteoblasts at remodeling sites undergo apoptosis. These senescent osteoblasts are rapidly cleared by immune cells, and due to the normal osteoblast proliferation cycle of 20-24 hours, fresh osteoblasts quickly occupy the vacated positions to continue regulating bone formation. Since osteoblast bone-forming capacity declines with age, senescent osteoblasts produce less bone than fresh ones [11-12], leading to enhanced bone formation and significantly increased bone mass as the final outcome of paradoxical bone formation.

2.2 Paradoxical Bone Formation and Osteoclasts

Osteoclasts are the sole cells involved in bone resorption. When osteocytes undergo apoptosis, osteoclasts can be recruited to clear the apoptotic cells [37]. Osteocytes differentiate from osteoblasts after bone formation is complete. Osteoclasts originate from monocyte-macrophage lineage cells, with their differentiation and activation primarily regulated by macrophage colony-stimulating factor (M-CSF) and the RANK/RANKL system, where RANKL belongs to the TNF superfamily [38-40]. M-CSF is essential for proliferation, survival, and differentiation of osteoclast precursors, as well as for osteoclast survival and cytoskeletal rearrangement required for bone resorption. Under M-CSF stimulation, monocytes differentiate into bone macrophages, which can further differentiate into osteoclasts with RANKL cooperation [37]. While traditional research suggested RANKL was secreted by osteoblasts, recent studies have identified osteocytes as the primary source of RANK. When osteocytes undergo apoptosis, ATP drives surrounding viable osteocytes to produce RANKL, recruiting osteoclasts and promoting their generation. In the presence of M-CSF, RANKL binding to its receptor facilitates recruitment of TNF receptor-associated factors (TRAFs), activating osteoclast-related signaling pathways [30,41-43] including NF- B, Akt, c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and MAPK. Additionally, osteoblasts remain important for osteoclast generation [44]; although osteoblast-derived RANKL is not the primary source for osteoclast differentiation, osteoblasts secrete osteoprotegerin (OPG) and promote M-CSF synthesis. OPG inhibits osteoclast differentiation and activation by binding RANKL and blocking its interaction with RANK, making the RANKL-RANK-OPG signaling axis crucial for bone homeostasis regulation. Osteoclast differentiation mechanisms are illustrated in Figure 2 [Figure 2: see original paper].

The first manifestation of paradoxical bone formation is osteoblast apoptosis. In balanced bone homeostasis, partial osteoblast apoptosis occurs at remodel-

ing sites, while remaining osteoblasts continue differentiating into osteocytes and other cells to participate in osteoclast generation regulation, ultimately balancing osteoblast-mediated bone formation with osteoclast-mediated bone resorption. If paradoxical bone formation is actively induced, it may influence osteoblast-to-osteocyte differentiation, thereby regulating osteoclast generation and enhancing OPG expression to inhibit osteoclast production, thus controlling further enhancement of bone resorption.

2.3 Paradoxical Bone Formation and Macrophages

Beyond the classic roles of osteoblasts and osteoclasts, bone homeostasis is also regulated by bone immunology, with increasing research focusing on macrophage modulation of bone homeostasis. Macrophages play important roles in bone homeostasis regulation [45-50], primarily through their effects on osteoblast differentiation and maturation to promote bone formation, and on osteoclast differentiation to promote bone resorption. Both macrophages and osteoclasts originate from monocytes, which differentiate into macrophages under M-CSF stimulation. With RANKL cooperation, macrophages can further differentiate into osteoclasts; however, inhibiting RANKL levels under normal M-CSF conditions suppresses osteoclast differentiation. Macrophages exist in two primary polarization states: classically activated macrophages (M1) and alternatively activated macrophages (M2). The M1 phenotype is generally considered pro-inflammatory, induced by Toll-like receptor (TLR) and interferon-γ (IFN-γ) signaling, releasing cytokines such as IL-1α, IL-1β, IL-6, IL-12, IL-23, TNF-α, and NO to defend against and eliminate pathogens. The M2 phenotype is considered anti-inflammatory, induced by Th2 cytokines like IL-4 and IL-13, releasing vascular endothelial growth factor A (VEGFA), BMP-2, IL-10, and TGF-β to suppress inflammatory responses and participate in inflammation resolution and tissue repair. Macrophage polarization is a complex process regulated by multiple pathways.

Studies have confirmed that M2 macrophages positively influence bone formation by promoting BMSC differentiation into osteoblasts [51-52]. When BMSCs are co-cultured with macrophages, macrophages polarize toward the M2 phenotype, which is considered a polarization state that promotes bone formation while inhibiting bone resorption. M2 polarization significantly upregulates BMP-2, TGF-β, and Osterix expression—all crucial factors for osteoblast differentiation. Additionally, M2 macrophages enhance VEGFA expression, which inhibits the PI3K/Akt signaling pathway [53] that promotes osteoclast differentiation, thereby suppressing bone resorption. Among M2-related cytokines, the IL-10 family includes IL-20, which inhibits NF- B and RANKL pathways, suppresses NFAT expression, inhibits IL-1β-mediated MAPK upregulation, and increases OPG and M-CSF expression. Through these regulatory actions, IL-20 ultimately promotes osteoblast generation and inhibits osteoclast differentiation, contributing to bone homeostasis [50].

When macrophages polarize to the M1 phenotype, they secrete various inflam-

matory factors, with IL-1 being most critical for bone homeostasis regulation, particularly in promoting osteoclast generation and bone resorption. IL-1 can directly downregulate OPG and upregulate RANKL expression. In RANKL-rich environments, IL-1β promotes osteoclast precursor development under MAPK pathway regulation and activates NF- B to upregulate RANKL expression, participating in osteoclast generation. IL-1 also influences osteoclast production by inducing release of other inflammatory cytokines such as TNF-α and IL-6. TNF-α promotes osteoclast generation by activating NF- B signaling and affecting RANKL, while IL-6 activates JAK/STAT, MAPK/ERK, PI3K-Akt, and NF- B pathways—key pathways for osteoclast generation [50,54]. M1 polarization enhances IL-1 expression, directly promoting osteoclast generation and amplifying its effects through other cytokines. Additionally, when M1 macrophages produce pro-inflammatory signals, they can trigger the COX-2-PGE2 pathway to exert anti-inflammatory effects and ultimately polarize toward M2. Mechanisms linking macrophage polarization with osteoblast and osteoclast differentiation are illustrated in Figure 3 [Figure 3: see original paper].

Macrophage recruitment and M2 polarization represent central aspects of paradoxical bone formation. In osteoporosis patients, inflammatory changes promote M1 polarization, creating a feedback loop that maintains chronic inflammation. Although macrophages actively polarize toward the anti-inflammatory M2 phenotype, this effect is minimal and cannot alter the dominant inflammatory state. However, actively inducing paradoxical bone formation through multiple mechanisms could enhance M2 polarization, shift the M1/M2 balance, control M1 polarization and its pro-inflammatory effects, strengthen M2 anti-inflammatory actions to modulate the inflammatory environment, and enhance M2 regulation of osteoblast differentiation while inhibiting osteoclast generation. This would ultimately enhance bone formation, suppress bone resorption, increase bone mass, and potentially reverse the bone homeostasis imbalance and bone loss characteristic of osteoporosis.

3 Paradoxical Bone Formation and Apoptosis

The key difference between paradoxical and normal bone formation lies in its mediation through osteoblast apoptosis to enhance bone formation. During this process, macrophage polarization toward the M2 phenotype increases bone formation. However, the precise mechanisms by which paradoxical bone formation controls macrophage M2 polarization remain under-investigated and may be closely related to macrophage efferocytosis of apoptotic osteoblasts.

3.1 Effect of Apoptosis on Macrophages

When paradoxical bone formation occurs, a subset of osteoblasts undergoes apoptosis. Macrophages are then recruited to engulf these apoptotic cells through efferocytosis, which polarizes them toward the M2 phenotype and ultimately enhances osteoblast differentiation. Apoptosis is a complex, multigene-controlled form of autonomous cell death essential for maintaining internal

homeostasis. Upon apoptotic signaling, cells undergo internal changes, first releasing "find-me" signals to recruit macrophages, followed by "eat-me" signals that initiate macrophage recognition and clearance [55]. This macrophage-mediated removal of apoptotic cells is termed "efferocytosis" [56-57]. Without efferocytosis, release of apoptotic cell contents could trigger inflammation, making efferocytosis generally considered anti-inflammatory [58].

During efferocytosis, macrophages block NF- B and TLR pathways, which generate cytokines like TNF-α and IL-6, thereby inhibiting M1 polarization. Additionally, when apoptotic cells are engulfed to form apoptotic bodies, receptors such as peroxisome proliferator-activated receptors (PPARs) are activated, promoting production of IL-10 and TGF-β—cytokines that facilitate M2 polarization. Studies confirm that when apoptosis recruits macrophages for clearance, proliferation of inflammatory M1 macrophages is not triggered, demonstrating that apoptosis-induced efferocytosis can modulate macrophage polarization, induce M2 polarization, generate related cytokines, and exert anti-inflammatory effects [56].

3.2 Effect of Osteoblast Apoptosis on Bone Formation

Current consensus holds that apoptosis is the ultimate fate of osteoblasts after bone formation is complete [13,59]. When osteoblasts undergo apoptosis, they release signals that rapidly recruit macrophages to perform efferocytosis. Bone tissue contains resident macrophages that maintain homeostasis, clear debris, and facilitate tissue repair—these are known as bone macrophages, which form coronal structures around osteoblasts. Consequently, when osteoblasts undergo apoptosis, bone macrophages can be quickly recruited and rapidly clear the apoptotic cells. Under efferocytosis, bone macrophages polarize toward the M2 phenotype, ultimately influencing bone formation [47].

As discussed previously, M2 macrophages and their associated cytokines promote bone formation by upregulating BMP-2, TGF-β, and Osterix expression to enhance BMSC-to-osteoblast differentiation, while inhibiting NFAT expression, MAPK and NF- B signaling pathways, enhancing VEGFA expression, and upregulating osteoblast-derived OPG to inhibit osteoclast production [37]. Theoretically, osteoblast apoptosis can promote macrophage recruitment and M2 polarization, stimulate BMSC-to-osteoblast differentiation, inhibit osteoclast production, positively influence bone formation, and suppress bone resorption. Since fresh osteoblasts produce more bone than senescent ones, inducing apoptosis in a subset of osteoblasts ultimately increases bone mass compared to pre-apoptosis levels, offering a new research direction and therapeutic approach for osteoporosis.

4 Potential of Paradoxical Bone Formation in Osteoporosis Treatment

Current osteoporosis treatment strategies primarily aim to increase bone density and mass by inhibiting osteoblast apoptosis while promoting their generation to enhance bone formation, and by suppressing osteoclast differentiation to reduce bone resorption. Paradoxical bone formation, which can ultimately increase bone formation, inhibit bone resorption, and increase bone mass, may represent a new therapeutic direction. In osteoporosis, the body maintains a chronic inflammatory microenvironment with elevated expression of TNF-α, IL-1, M-CSF, and PGE2—cytokines that promote M1 polarization and activate osteoclast differentiation pathways, increasing bone resorption. While M1-derived pro-inflammatory signals can trigger the COX-2-PGE2 pathway to promote anti-inflammatory effects and M2 polarization, secreting IL-4, IL-10, IL-13 and increasing VEGF, BMP-2, TGF-β, and Osterix expression to inhibit JAK/STAT and activate TLR/NF- B, JNK, and BMP/Smad pathways, the persistent inflammatory microenvironment and strong inflammatory factor expression primarily drive M1 polarization, preventing macrophages from actively controlling osteoporosis progression.

Based on the natural condition where half of osteoblasts undergo apoptosis at bone remodeling sites, actively inducing paradoxical bone formation could potentially reverse osteoporosis. By promoting apoptosis in a subset of osteoblasts, macrophages are recruited and clear apoptotic cells through efferocytosis, polarizing toward M2. This upregulates BMP-2, TGF-β, and Osterix expression while inhibiting NFAT, MAPK, NF- B signaling, enhancing VEGFA expression, and increasing OPG production, ultimately inhibiting further osteoclast generation and controlling bone resorption. Simultaneously, it promotes BMSC-to-osteoblast differentiation, allowing fresh osteoblasts to rapidly replace senescent ones, enhancing both bone formation and bone mass, and ultimately correcting the imbalanced bone resorption-formation dynamics and bone loss in osteoporosis. Experimental evidence has confirmed that pro-apoptotic treatment of less than 50% of osteoblasts increases vertebral bone mass, bone surface macrophages, and BMSCs, with positive correlation between macrophage and BMSC numbers, while osteoclast numbers remain unchanged—validating the feasibility of paradoxical bone formation as a potential new osteoporosis therapy [8].

Osteoporosis-related mechanisms are illustrated in Figure 4 [Figure 4: see original paper].

Osteoporosis is a prevalent clinical condition that historically affected individuals over 50 and postmenopausal women but now occurs across all age groups due to unhealthy lifestyles and adverse effects of other disease treatments, remaining a major research focus. While current treatments increase bone density by inhibiting osteoblast apoptosis and osteoclast differentiation, deeper understanding of osteoblast apoptosis' s role in bone homeostasis has led to the paradoxical

bone formation concept. This approach promotes partial osteoblast apoptosis, recruits macrophages for efferocytosis and M2 polarization, generates factors that promote osteoblast differentiation while inhibiting osteoclast generation, replaces senescent osteoblasts with fresh ones, and controls bone resorption to delay osteoporosis progression. Because fresh osteoblasts form more bone than senescent ones, this partial apoptosis increases bone mass, offering a potential new therapeutic pathway.

However, experimental validation of paradoxical bone formation for increasing bone mass in osteoporosis remains limited. Currently identified apoptosis pathways include the membrane receptor pathway (Fas/FasL), the mitochondrial pathway involving cytochrome C release, and endoplasmic reticulum stress (ERS), all ultimately activating caspases through cascading reactions to induce apoptosis [57,60]. Precisely controlling the proportion of osteoblast apoptosis without harming other cells remains experimental. Furthermore, different tissues exhibit varying apoptotic responses to the same stimuli, making it challenging to precisely control osteoblast apoptosis across the entire body at consistent ratios. This requires continuous experimental exploration and validation. Therefore, "paradoxical bone formation for osteoporosis treatment" remains theoretical. Nevertheless, as research progresses, the specific mechanisms of paradoxical bone formation in osteoporosis treatment will gradually be elucidated, potentially providing additional therapeutic options [61].

Author Contributions

YANG Yang and GAO Xi conceptualized and designed the article. YANG Yang collected and organized literature, and drafted the manuscript. GAO Xi conducted feasibility analysis, revised the manuscript, was responsible for quality control and final review, and provided overall supervision.

Conflict of Interest

The authors declare no conflicts of interest.

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(Received: December 10, 2024; Revised: April 6, 2025)
(Editor: JIA Mengmeng)

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