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BONE MARROW AND ADIPOSE TISSUE (G DUQUE AND B LECKA-CZERNIK, SECTION EDITORS)

Bone Marrow Adipose Tissue and Skeletal Health

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Abstract

Purpose of Review To summarize and discuss recent progress and novel signaling mechanisms relevant to bone marrow adipocyte formation and its physiological/pathophysiological implications for bone remodeling.

Recent Findings Skeletal remodeling is a coordinated process entailing removal of old bone and formation of new bone. Several bone loss disorders such as osteoporosis are commonly associated with increased bone marrow adipose tissue. Experimental and clinical evidence supports that a reduction in osteoblastogenesis from mesenchymal stem cells at the expense of adipogenesis, as well as the deleterious effects of adipocyte-derived signaling, contributes to the etiology of osteoporosis as well as bone loss associated with aging, diabetes mellitus, post-menopause, and chronic drug therapy. However, this view is challenged by findings indicating that, in some contexts, bone marrow adipose tissue may have a beneficial impact on skeletal health.

Summary Further research is needed to better define the role of marrow adipocytes in bone physiology/pathophysiology and to determine the therapeutic potential of manipulating mesenchymal stem cell differentiation.

Keywords Adipocyte · Bone · Differentiation · Mesenchymal stem cell · Osteoblast

Introduction

Bone marrow is a heterogeneous and dynamic tissue that undergoes significant alterations in structure and composition with age, exposure to therapeutic drugs, physiological changes, and several pathological states. Bone marrow adipose tissue reflects the accrual of adipocytes embedded within a complex extracellular matrix along with cells of both the hematopoietic and mesenchymal lineage. Adipocytes are one of the most abundant cell types (15–70%) within human bone marrow [1, 2] and changes in the number and size of bone marrow adipocytes are well established to occur with aging and several clinical disorders of bone loss such as osteoporosis. Consequently, considerable attention has been directed to investigating the impact of bone marrow adipocytes on the critical physiological process of bone remodeling as well as the relevance of these cells to bone loss disorders [3••, 4]. Bone marrow mesenchymal stem cells (MSCs) are a population of self-renewing pluripotent stem cells with the ability to give rise to adipocytes or bone-forming osteoblasts. Hematopoietic stem cells (HSCs) give rise to blood cells of the lymphoid and myeloid lineage as well as bone-resorbing osteoclasts [5, 6]. Adipocytes have been found to influence bone remodeling by influencing osteoblast and osteoclast differentiation and function [5]. As a coordinated balance between bone formation and resorption is critical to maintain skeletal integrity, bone marrow adipocytes may play roles both in homeostatic bone remodeling as well as bone loss disorders. In this brief review, we will highlight recent advances in understanding the role of bone marrow adipocytes in contributing to the deregulation of osteoblast and osteoclast differentiation that affects bone remodeling under pathological conditions.

This article is part of the Topical Collection on *Bone Marrow and Adipose Tissue*

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Cell-Intrinsic Suppression of Osteoblastogenesis

A considerable body of fundamental experimental evidence derived from cell and animal studies indicates adipocytes can

affect the development and function of osteoblasts and osteoclasts and thereby bone remodeling [5]. As osteoblasts and adipocytes are derived from a common MSC precursor, one of the principal mechanisms believed to account for this is an intrinsic effect on MSC lineage allocation. The lineage fate of MSCs is determined both by activation of cell signaling pathways leading to a terminally differentiated cell type as well as active suppression of competitive lineages [7–9]. For example, the profound osteogenic influence of Wingless-type MMTV integration site family (Wnt) signaling derives both from the induction of osteoblastogenic transcription factors such as runt-related transcription factor 2 (RUNX2) and osterix [10, 11] and the active suppression of competing lineages from MSCs [6, 12]. Most notably, Wnt signaling reduces the expression and activity of the potent adipogenic transcription factors peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT/enhancer binding protein α (C/EBPα) in MSCs and thereby, inhibits adipocyte formation [12, 13]. Similarly, MSC adipogenesis entails both stimulation of adipogenic signaling and suppression of osteogenic pathways such as Wnt and Notch [14–16]. For example, the induction and accumulation of intracellular proteins such as transducing-like enhancer of split 3 (TLE3) with adipogenic differentiation of bone marrow stromal cells was recently reported to suppress the osteogenic signaling through synergistic enhancement of PPARγ activity and repression of ß-catenin and RUNX2 in a histone deacetylase-dependent fashion [17, 18]. As such, factors that influence MSC lineage allocation can have a profound influence on the balance of cell types present within bone and thus skeletal homeostasis. It is well known that bone marrow adipose tissue increases with age and that reduced bone quantity and quality (i.e., osteopenia or osteoporosis) related to aging [19], menopause [20], diabetes [21, 22], chronic glucocorticoid exposure [23, 24], and anorexia nervosa [25] is frequently associated with elevated bone marrow adipocytes. This indicates at the very least that changes in the physiological milieu that coincides with these states result in greater relative predisposition for MSC adipogenesis versus osteoblastogenesis.

Influence of Adipocyte-Secreted Signaling Molecules on Bone Remodeling

As introduced previously, adipocytes are generally abundant in human bone marrow [1, 2] and expansion of bone marrow adipose tissue is common with aging and several clinical bone loss disorders. Aside from intrinsic effects on MSC differentiation, adipocytes have the potential to impact the development and function of other cell types in bone through the paracrine actions of secreted biologically active signaling molecules (adipokines). Several studies have reported that adipocyte-conditioned media samples suppress the formation of osteogenic lineages from MSCs [26–28] and promote osteoclast formation from HSCs [5, 29]. This indicates that adipocyte-derived factors can influence the development of key effectors of bone remodeling and thereby bone mass and skeletal integrity. Over the past decade, several key inhibitors of osteoblast differentiation were identified as adipokines secreted by bone marrow adipocytes. For instance, preadipocytes secrete the Wnt inhibitor, secreted frizzled-related protein 1 (sFRP-1) that directs MSC fate decision toward the adipogenic lineage and inhibits osteogenesis in response to inhibition of Wnt/β-catenin signaling [28]. Legumain, a cysteine protease secreted in increasing amounts with MSC adipogenic differentiation, has been shown to suppress osteoblast commitment and maturation concomitant with inducing adipogenic differentiation of undifferentiated cells in a paracrine/autocrine fashion [30]. Mechanistically, the degradation of fibronectin by legumain prevents extracellular matrix deposition essential for osteogenesis and provides a microenvironment more amenable to bone marrow adipogenesis. The nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB) binding regions in legumain promoter is thought to be activated to induce legumain expression during the progression of adipogenic differentiation [30]. Consequently, legumain expression was found to be markedly induced in MSCs isolated from osteoporotic individuals suggesting a potential target to treat the condition [30].

Previously, we reported that bone marrow adipocytes secrete large amounts of chemerin and that this adipokine promotes MSC adipogenesis while suppressing osteoblastogenesis [31]. Chemerin activation of its cognate receptor chemokine-like receptor 1 (CMKLR1) in bone marrow MSCs resulted in PPARγ-mediated β-catenin ubiquitination that abrogated basal osteogenic Wnt signaling and promoted the adipogenic PPARγ signaling in MSCs [32, 33•]. In addition, the paracrine actions of chemerin through activation of CMKLR1 expressed by HSCs promoted osteoclastogenic differentiation and matrix resorption [29]. Conversely, other adipokines such as C1q/tumor necrosis factor (TNF)-related protein-3 (CTRP3) inhibit osteoblast-mediated osteoclastogenic differentiation thereby disrupting the coordination between bone formation and resorption [34]. Subfatin (METRNL) is another novel adipokine induced during adipogenesis [35] that has been reported to impair osteoblast differentiation and maturation [36]. Although these adipogenic factors oppose osteoblast development, other factors such as the bone morphogenetic proteins (BMPs) can stimulate both adipogenic and osteoblastogenic differentiation. For example, BMP7 (also known as osteogenic protein-1) has been shown to induce the proliferation and differentiation of adipocytes and osteoblasts in mouse bone marrow stromal cell cultures [37]. One possible mechanism could be through the activation of alternate receptors depending on the conditions prevailing in the microenvironment. For example, while BMP receptor type IA (BMPR-IA) activates adipogenic

pathways, the type IB BMPR (BMPR-IB) favors osteoblastogenesis [6]. However, the adipocyte-secreted factors exhibit a predominant influence in suppressing osteoblastogenic BMP signaling by activating the NF-κB pathway [26] suggesting that the suppression of adipogenic factors is essential for BMP osteoblast differentiation.

Recently, there has been increasing interest in the role of adenosine-mediated purinergic signaling on bone marrow adipogenesis and bone metabolism. Experimental evidence indicates that MSCs are both a source of adenosine within the marrow microenvironment and a target for adenosine signaling through the expression of purinergic receptors that influence fundamental cellular processes including MSC self-renewal, differentiation, and survival [38–42]. MSCs express significant levels of the ectoenzymes ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1; CD39) and 5′ nucleotidase (CD73) which produce adenosine through the sequential degradation of extracellular ATP. Adenosine has been shown to promote both osteoblastogenic and adipogenic MSC differentiation depending upon the subtype of adenosine receptor activated [41–43]. For example, adenosine stimulation of $A_{2B}R$ promotes MSC osteogenesis at the expense of adipogenesis by stimulating cyclic AMP (cAMP) while the cAMP inhibitory adenosine receptors such as $A_{1A}R$ and $A_{3A}R$ suppress osteogenesis by promoting adipogenesis [43–47]. Contrastingly, although the cAMP stimulatory $A_{2A}R$ induces osteogenesis at the late osteoblast stage of differentiation, it promotes adipogenesis in undifferentiated MSCs [43]. Furthermore, at the basal level, the degradation of ATP by the expression of CD39 and CD73 is a prerequisite to block ATP-mediated adipogenic signaling and activate adenosine-induced osteogenic differentiation [48]. Mechanistically, this has been shown to entail ATP binding and activation of the P2 subtype purinergic receptor which promotes PPARγ expression. On the other hand, conversion of ATP to adenosine by CD39 and CD73 is a prerequisite for activation of P1 subtype receptors that promote RUNX2 expression [46, 47, 49]. Studies also suggest that the adenosine-producing ectoenzymes and the purinergic receptors mutually influence each other to establish regulatory circuits that maintain MSCs [46, 50]. For instance, a loss of CD73 mRNA expression was observed in $A_{2A}R$ knockout mouse MSCs and conversely $A_{2A}R$ mRNA expression was downregulated in CD73 knockout mouse MSCs [46]. Although the mechanisms involved in this interplay are unknown, it is likely that the adipogenic $A_{2A}R$ expression [43] is coordinately regulated with osteogenic CD73 expression [41] to maintain stemness. In the context of osteoclast differentiation, all four adenosine receptors A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R were found to be expressed in osteoclast precursors and further induced by osteoclastogenic stimuli [51–55]. Similar to that in MSCs, these receptors exhibit differential effects on HSC differentiation. For example, while A_1R promotes osteoclast differentiation, activation of $A_{2A}R$ blocks osteoclastogenesis [54, 55]. Also similar to that in MSCs, HSCs express high levels of ectonucleotidases (CD39 and CD73) that can shift HSCs from ATP-induced granulocyte-macrophage differentiation program [56] to adenosine-induced osteoclast differentiation program [52, 53].

In addition to contributing to the de novo generation of adenosine by metabolizing extracellular ATP, bone marrow stem cells can influence levels of extracellular adenosine and thereby local purinergic signaling through the expression of equilibrative adenosine transporters at the cell membrane. Evidently, loss of the equilibrative nucleoside transporter 1 (ENT1) in mice increases extracellular adenosine levels by preventing the transport of adenosine into cells that promotes activation of P1 receptors [42, 57]. Consequently, osteoblast marker gene expression and osteoblast differentiation increases in ENT1 null mice [42, 57]. However, ENT1-null mice manifest an osteopenic phenotype with increased bone turnover [57–59] perhaps due to a dominant effect of ENT1 on osteoclast formation than osteoblast differentiation [57]. Mirroring these effects, loss of function ENT1 mutations also impairs bone homeostasis in humans [59]. Conversely, mutations in an acidic pH-dependent lysosomal adenosine transporter ENT3 [60] result in reduced resorptive abilities of osteoclasts leading to dysosteosclerosis, a form of osteopetrosis in humans [61]. Together, these findings signify that both intra- and extracellular adenosine can differentially influence bone marrow stem cell differentiation and bone remodeling.

Does Clinical Evidence Support a Role for Adipocytes in Skeletal Health?

The presence of adipose tissue in the bone marrow of healthy individuals with no evidence of pathological bone loss raises the fundamental question of whether there is physiological role for adipocytes in the maintenance of skeletal integrity. For example, consistent with the role of peripheral adipose depots, it is possible that marrow adipocytes through the uptake of fatty acids may protect other cells in the local microenvironment from potential lipotoxicity and/or serve as a mobilizable reservoir that can be accessed during periods of energy deficit [62]. Moreover, under physiological conditions, marrow fat has a positive association with bone mass. However, this may be related more to the nature rather than the quantity of marrow adipose. For example, during puberty and with fracture repair processes, marrow fat exhibits a brown adipocyte-like phenotype characterized by the expression of brown adipocyte transcription factors (e.g., PR domain containing 16 (Prdm16) and Forkhead Box C2 (FoxC2)) and marker genes (e.g., PGC1α, deiodinase 2 (Dio2), beta-3-adrenergic receptor (β3AR), and uncoupling protein 1 (UCP1)) [1, 4, 63, 64]. It is generally believed that marrow

adipocytes exhibiting brown adipocyte-like phenotype contribute to a microenvironment favorable for osteogenesis by providing the necessary energy balance, adaptive thermogenesis, and/or by releasing pro-osteogenic factors such as insulin-like growth factor 1 (IGF1) and leptin [1, 4, 64, 65]. In support of this, adipocyte-specific FoxC2 overexpression in mice or ectopic expression of FoxC2 in cultured bone marrow-derived adipocytes induced the browning of adipocytes and promoted the secretion of paracrine bone anabolic factors such as insulin-like growth factor binding protein 2 (IGFBP2) and wingless related MMTV integration site 10b (WNT10b) leading to enhanced osteogenesis and increased bone mass [66••].

On the other hand, there is substantive and consistent evidence from clinical studies that conditions associated with bone loss, such as osteoporosis, aging, and glucocorticoid therapy, are commonly associated by an adipose-rich bone marrow [2, 5, 6, 67]. It is postulated that in addition to a general expansion of adipose volume, bone marrow adipocytes under these conditions lose their brown adipose tissue characteristics which contributes to the increased production of factors such as inflammatory cytokines and free fatty acids that suppress osteogenic differentiation of MSCs [1]. This shift in the impact of marrow adipocytes on bone remodeling between physiological and pathological conditions is thought to arise from sensing and transducing stress responses during disease conditions. A common condition associated with most diverse disease processes affecting bone remodeling is oxidative stress which can contribute to a switch from a brown to white adipocyte-like phenotype in bone marrow adipose tissue [68–71]. For example, it has been reported that proteins which inactivate reactive oxygen species (ROS) such as antioxidant enzymes and UCP1 were induced during differentiation of brown adipocytes [72]. However, increased production of ROS by pro-inflammatory cytokines could overwhelm the antioxidant capacity of these cells resulting in downregulation of the classical brown adipocyte markers such as UCP1 and β-Klotho [72]. Experimental evidence also supports that oxidative stress and the switch from a brown adipocyte phenotype can also contribute to the expansion of the bone marrow adipose tissue commonly observed with bone loss disorders such as osteoporosis. For example, the elevated oxidative stress can lead to an increasing dependence on alternate cellular defense mechanisms such as FoxO transcription factors that require β-catenin for activation [73, 74•]. The resulting diversion of β-catenin to FoxO-mediated transcription in response to oxidative stress is believed to lead to reduced T-cell factor/lymphoid enhancer-binding factor (TCF/LEF)-mediated osteogenic signaling in MSCs [73]. This loss of β-catenin with oxidative stress further relieves functional repression of the master adipogenic transcription factor, PPARγ that promotes adipogenesis and negatively associates with bone mass [75].

Despite compelling evidence from cell-based models, the impact of marrow adipose tissue on skeletal homeostasis or bone loss disorders is less clear owing to inconsistencies in findings from clinical studies [76, 77]. This challenge to the classical view on the inverse association between adipogenic and osteoblastogenic signaling is further bolstered by reports of a lack of association between marrow adiposity and skeletal phenotypes in animal models such as loss of function mutations in kit receptor [78] and 11beta-hydroxysteroid dehydrogenase 1 (11 β-HSD1) enzyme [79] or in some mouse strains such as C3H/HeJ [80]. Thus, the type of correlation between bone marrow adipocytes and bone formation cannot be generalized and appears to vary with the nature of stimuli driving MSC adipogenesis and the physiological/pathophysiological context. Furthermore, the development and mass of bone marrow adipose tissue are distinct from those of peripheral adipose depots which under pathological conditions are often found to be negatively associated with the marrow adiposity [81]. For instance, type I diabetes, malnutrition, anorexia nervosa, calorie restriction, and lipodystrophy exhibit reduction in peripheral adipose depots but an inverse increase in marrow adiposity [82, 83]. However, even this relationship between bone marrow and peripheral adiposity also cannot be generalized as there are other scenarios such as growth hormone deficiency where positive correlation exists between the developments of these adipose depots [84].

Impact of Therapeutic Drugs on Bone Remodeling

In addition to endogenous adipocyte-secreted factors, several therapeutic drugs are known to influence the balance between adipogenesis and osteoblastogenesis by targeting the adipogenic and/or osteogenic signals. For example, antidiabetic drugs such as thiazolidinedione and steroidal anti-inflammatory agents are well-known inducers of PPARγ and thereby suppress osteogenesis and promote adipogenesis of MSCs. Consistent with this, the clinical use of these drugs has been reported in several analyses to be associated with both decreased bone formation and enhanced bone resorption [85–87] as well as an increased risk for bone fracture [87]. Glucocorticoids are commonly used for the chronic treatment of rheumatic diseases [88, 89]. These drugs cause an increased production of receptor activator of nuclear factor-kappa B ligand (RANKL) in osteogenic cells that promotes osteoclastogenesis and ultimately leads to accelerated bone resorption. Steroidal anti-inflammatory drugs also suppress the production of cytokines, TGFβ and BMP2, and induce the adipogenic transcription factors, CEBP α, CEBPβ, and PPARγ, that drive the adipogenesis at the expense of osteogenic differentiation [88, 89]. Chronic treatment with anticancer/antiviral nucleoside analogs (zidovudine, 5-

fluorouracil, tenofovir, emtricitabine, ritonavir) that compete with natural nucleosides for transport and/or incorporation into DNA, modulate intracellular or extracellular availability of nucleosides, and have been reported to induce bone marrow adipogenesis and bone loss [90–94]. Consistent with the established increased risk for bone loss with menopause, drugs that reduce estrogen levels, such as medroxyprogesterone acetate which is widely used for treating endometriosis and as a contraceptive agent, can lead up to 8% bone loss depending on the dose and extent of administration [95]. Similarly, aromatase inhibitors such as anastrozole, exemestane, and letrozole which are used as hormone therapy for estrogen receptor-positive breast cancer also drastically reduce estrogen levels and cause marked bone loss (2% bone loss per year compared with 1% loss in post-menopausal women) [96].

In addition to adverse actions on bone tissue, drugs used for treating bone disorders can negatively influence bone marrow fat. Intriguingly, a number of antiresorptive and anabolic drugs that increase bone mass also exhibit a general inverse relationship with bone marrow fat [97–102]. For example, despite the therapeutic benefits of bisphosphonates being directed toward osteoclast inhibition, certain drugs within this class, including residronate and zoledronic acid, suppress bone marrow fat [97–99]. In addition, anabolic agents that target osteoblast development/function have also been shown to reduce marrow fat formation [100–102]. Notably, teriparatide reduces fat accumulation in bone marrow but not in white adipose tissue [100, 101]. Thus, understanding how drugs can act on bone marrow fat is a fundamental challenge that has the potential for developing effective therapeutic applications.

Therapeutic Implications

Antiresorptive therapy is the most common approach to treating bone loss disorders such as osteoporosis and agents with this mechanism of action generally fall under five categories: bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), monoclonal antibodies (e.g., denosumab), and calcitonin. Among these, bisphosphonates are the most typically used first-line antiresorptive agents owing to a long history of clinical experience, relatively low cost, and established benefit to reduce fracture risk. However, while studies examining the long-term safety and efficacy in different categories of patient subpopulations are still ongoing [103], the improved antifracture efficacy and safety profile of denosumab to date have contributed to a rapid and increasing clinical adoption of the use of this drug for osteoporosis. In general, the principal antiresorptive therapy is to re-establish the balance of bone remodeling through a relative improvement in bone formation secondary to inhibition of bone resorption. In contrast to these agents, anabolics such as parathyroid hormone (PTH) and teriparatide directly stimulate bone formation resulting in a rapid increase in bone mass. Although these drugs are approved for the treatment of bone loss disorders such as osteoporosis, cost and concerns regarding increased long-term risk for adverse effects, such as osteosarcoma, have limited the clinical application of these agents [104]. Moreover, while anabolics enhance bone formation, with prolonged use they also can increase the overall rate of bone turnover by activating MSCs and osteoblasts to release pro-osteoclastogenic signaling molecules that stimulate bone resorption with prolonged use. Therefore, activation of bone formation needs to be coupled with a reduced resorption in order to promote bone regeneration in osteoporotic individuals. This has led to the exploration of combination therapy or a sequential anabolic followed by antiresorptive therapy to improve the efficacy and overcome the limitations of monotherapy with antiresorptives or anabolics [105–108]. However, with newfound knowledge gained from research in bone marrow fat, it is tempting to speculate that interventions promoting osteoblastogenic versus adipogenic MSC differentiation, transdifferentiation of existing marrow adipocytes into osteoblasts, and/or white-to-brown conversion of marrow adipocytes could offer novel and effective therapeutic avenues. Outcomes from recent preclinical studies supporting this preposition are also encouraging in this direction [66••, 109].

Summary

In conclusion, a well-established body of clinical literature supports an association between bone marrow adipose tissue and bone loss attributed to aging, menopause, and drugs. Similarly, considerable experimental evidence from animal and cell culture models provides a mechanistic basis for rationalizing the deleterious effects of bone marrow adipocytes on the development and function of other bone cell types. However, this view is complicated by studies indicating that marrow adipose tissue may be largely inconsequential, or in some cases, beneficial. As such, it is becoming increasingly apparent that our view of bone marrow adipose tissue must go beyond a limited consideration of volume to consider other factors such as adipocyte phenotype (e.g., brown versus white) and the physiological/pathophysiological context. Recent studies reveal that antioxidant defenses associated with acquiring brown fat feature as one possible cause for the positive association between bone marrow adipose tissue and bone mass under physiological states (e.g., puberty and fracture repair). However, further studies are required to improve understanding of the mechanisms that contribute to transition between the potential beneficial physiological and deleterious pathological effects of bone marrow adipose tissue. Ultimately, this may lead to novel therapies for bone loss disorders that modulate the lineage determination (adipocytes versus osteoblasts) of mesenchymal stem cells and/or phenotype of marrow adipocytes (white versus brown).

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Compliance with Ethical Standards

Conflict of Interest Muruganandan Shanmugam and Rajgopal Govindarajan declare no conflict of interest. Christopher Sinal reports grants from Canadian Institutes of Health Research and the National Sciences and Engineering Research Council, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kawai M, de Paula FJ, Rosen CJ. New insights into osteoporosis: the bone-fat connection. J Intern Med. 2012;272:317–29.
2. Meunier P, Aaron J, Edouard C, Vignon G. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue. A quantitative study of 84 iliac bone biopsies. Clin Orthop Relat Res. 1971;80:147–54.
3.•• Ambrosi TH, Scialdone A, Graja A, Gohlke S, Jank AM, Bocian C, et al. Adipocyte accumulation in the bone marrow during obesity and aging impairs stem cell-based hematopoietic and bone regeneration. Cell Stem Cell. 2017;20:771–784 e776. **This study characterizes changes in cell state and cell surface marker profiles of bone marrow-resident stem cells during bone cell fate decision.**
4. Krings A, Rahman S, Huang S, Lu Y, Czernik PJ, Lecka-Czernik B. Bone marrow fat has brown adipose tissue characteristics, which are attenuated with aging and diabetes. Bone. 2012;50:546–52.
5. Muruganandan S, Sinal CJ. The impact of bone marrow adipocytes on osteoblast and osteoclast differentiation. IUBMB Life. 2014;66:147–55.
6. Muruganandan S, Roman AA, Sinal CJ. Adipocyte differentiation of bone marrow-derived mesenchymal stem cells: cross talk with the osteoblastogenic program. Cell Mol Life Sci. 2009;66:236–53.
7. Sun H, Kim JK, Mortensen R, Mutyaba LP, Hankenson KD, Krebsbach PH. Osteoblast-targeted suppression of PPARgamma increases osteogenesis through activation of mTOR signaling. Stem Cells. 2013;31:2183–92.
8. Lecka-Czernik B, Suva LJ. Resolving the two "bony" faces of PPAR-gamma. PPAR Res. 2006;2006:27489.
9. Kveiborg M, Sabatakos G, Chiusaroli R, Wu M, Philbrick WM, Horne WC, et al. DeltaFosB induces osteosclerosis and decreases adipogenesis by two independent cell-autonomous mechanisms. Mol Cell Biol. 2004;24:2820–30.
10. Nakashima K, Zhou X, Kunkel G, Zhang Z, Deng JM, Behringer RR, et al. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. Cell. 2002;108:17–29.
11. Komori T. Regulation of bone development and extracellular matrix protein genes by RUNX2. Cell Tissue Res. 2010;339:189–95.
12. Liu J, Farmer SR. Regulating the balance between peroxisome proliferator-activated receptor gamma and beta-catenin signaling during adipogenesis. A glycogen synthase kinase 3beta phosphorylation-defective mutant of beta-catenin inhibits expression of a subset of adipogenic genes. J Biol Chem. 2004;279:45020–7.
13. Kawai M, Mushiake S, Bessho K, Murakami M, Namba N, Kokubu C, et al. Wnt/Lrp/beta-catenin signaling suppresses adipogenesis by inhibiting mutual activation of PPARgamma and C/EBPalpha. Biochem Biophys Res Commun. 2007;363:276–82.
14. Song L, Liu M, Ono N, Bringhurst FR, Kronenberg HM, Guo J. Loss of wnt/beta-catenin signaling causes cell fate shift of preosteoblasts from osteoblasts to adipocytes. J Bone Miner Res. 2012;27:2344–58.
15. Kang S, Bennett CN, Gerin I, Rapp LA, Hankenson KD, Macdougald OA. Wnt signaling stimulates osteoblastogenesis of mesenchymal precursors by suppressing CCAAT/enhancer-binding protein alpha and peroxisome proliferator-activated receptor gamma. J Biol Chem. 2007;282:14515–24.
16. Takada I, Kouzmenko AP, Kato S. Wnt and PPARgamma signaling in osteoblastogenesis and adipogenesis. Nat Rev Rheumatol. 2009;5:442–7.
17. Kokabu S, Nguyen T, Ohte S, Sato T, Katagiri T, Yoda T, et al. TLE3, transducing-like enhancer of split 3, suppresses osteoblast differentiation of bone marrow stromal cells. Biochem Biophys Res Commun. 2013;438:205–10.
18. Villanueva CJ, Waki H, Godio C, Nielsen R, Chou WL, Vargas L, et al. TLE3 is a dual-function transcriptional coregulator of adipogenesis. Cell Metab. 2011;13:413–27.
19. Justesen J, Stenderup K, Ebbesen EN, Mosekilde L, Steiniche T, Kassem M. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. Biogerontology. 2001;2:165–71.
20. Yeung DK, Griffith JF, Antonio GE, Lee FK, Woo J, Leung PC. Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: a proton MR spectroscopy study. J Magn Reson Imaging. 2005;22:279–85.
21. Botolin S, McCabe LR. Bone loss and increased bone adiposity in spontaneous and pharmacologically induced diabetic mice. Endocrinology. 2007;148:198–205.
22. Piccinin MA, Khan ZA. Pathophysiological role of enhanced bone marrow adipogenesis in diabetic complications. Adipocyte. 2014;3:263–72.
23. Wang FS, Lian WS, Weng WT, Sun YC, Ke HJ, Chen YS, et al. Neuropeptide Y mediates glucocorticoid-induced osteoporosis and marrow adiposity in mice. Osteoporos Int. 2016;27:2777–89.
24. Ko JY, Chuang PC, Ke HJ, Chen YS, Sun YC, Wang FS. MicroRNA-29a mitigates glucocorticoid induction of bone loss and fatty marrow by rescuing Runx2 acetylation. Bone. 2015;81:80–8.
25. Bredella MA, Fazeli PK, Miller KK, Misra M, Torriani M, Thomas BJ, et al. Increased bone marrow fat in anorexia nervosa. J Clin Endocrinol Metab. 2009;94:2129–36.
26. Abdallah BM. Marrow adipocytes inhibit the differentiation of mesenchymal stem cells into osteoblasts via suppressing BMP-signaling. J Biomed Sci. 2017;24:11.
27. Abdallah BM, Kassem M. New factors controlling the balance between osteoblastogenesis and adipogenesis. Bone. 2012;50:540–5.
28. Taipaleenmaki H, Abdallah BM, AlDahmash A, Saamanen AM, Kassem M. Wnt signalling mediates the cross-talk between bone

marrow derived pre-adipocytic and pre-osteoblastic cell populations. Exp Cell Res. 2011;317:745–56.
29. Muruganandan S, Dranse HJ, Rourke JL, McMullen NM, Sinal CJ. Chemerin neutralization blocks hematopoietic stem cell osteoclastogenesis. Stem Cells. 2013;31:2172–82.
30. Jafari A, Qanie D, Andersen TL, Zhang Y, Chen L, Postert B, et al. Legumain regulates differentiation fate of human bone marrow stromal cells and is altered in postmenopausal osteoporosis. Stem Cell Reports. 2017;8:373–86.
31. Muruganandan S, Roman AA, Sinal CJ. Role of chemerin/CMKLR1 signaling in adipogenesis and osteoblastogenesis of bone marrow stem cells. J Bone Miner Res. 2010;25:222–34.
32. Muruganandan S, Parlee SD, Rourke JL, Ernst MC, Goralski KB, Sinal CJ. Chemerin, a novel peroxisome proliferator-activated receptor gamma (PPARgamma) target gene that promotes mesenchymal stem cell adipogenesis. J Biol Chem. 2011;286:23982–95.
33.• Muruganandan S, Govindarajan R, McMullen NM, Sinal CJ. Chemokine-like receptor 1 is a novel Wnt target gene that regulates mesenchymal stem cell differentiation. Stem Cells. 2017;35:711–24. **This study identifies a negative feedback loop operating through chemerin system that can tip cell fate decisions between adipocytes and osteoblasts in bone marrow stem cells.**
34. Kim JY, Min JY, Baek JM, Ahn SJ, Jun HY, Yoon KH, et al. CTRP3 acts as a negative regulator of osteoclastogenesis through AMPK-c-Fos-NFATc1 signaling in vitro and RANKL-induced calvarial bone destruction in vivo. Bone. 2015;79:242–51.
35. Li ZY, Zheng SL, Wang P, Xu TY, Guan YF, Zhang YJ, et al. Subfatin is a novel adipokine and unlike Meteorin in adipose and brain expression. CNS Neurosci Ther. 2014;20:344–54.
36. Gong W, Liu Y, Wu Z, Wang S, Qiu G, Lin S. Meteorin-like shows unique expression pattern in bone and its overexpression inhibits osteoblast differentiation. PLoS One. 2016;11:e0164446.
37. Chen TL, Shen WJ, Kraemer FB. Human BMP-7/OP-1 induces the growth and differentiation of adipocytes and osteoblasts in bone marrow stromal cell cultures. J Cell Biochem. 2001;82:187–99.
38. Burnstock G, Ulrich H. Purinergic signaling in embryonic and stem cell development. Cell Mol Life Sci. 2011;68:1369–94.
39. Ferrari D, Gulinelli S, Salvestrini V, Lucchetti G, Zini R, Manfredini R, et al. Purinergic stimulation of human mesenchymal stem cells potentiates their chemotactic response to CXCL12 and increases the homing capacity and production of proinflammatory cytokines. Exp Hematol. 2011;39:360–74. 374 e361–365
40. Kaunitz JD, Yamaguchi DT. TNAP, TrAP, ecto-purinergic signaling, and bone remodeling. J Cell Biochem. 2008;105:655–62.
41. Takedachi M, Oohara H, Smith BJ, Iyama M, Kobashi M, Maeda K, et al. CD73-generated adenosine promotes osteoblast differentiation. J Cell Physiol. 2012;227:2622–31.
42. He W, Mazumder A, Wilder T, Cronstein BN. Adenosine regulates bone metabolism via A1, A2A, and A2B receptors in bone marrow cells from normal humans and patients with multiple myeloma. FASEB J. 2013;27:3446–54.
43. Gharibi B, Abraham AA, Ham J, Evans BA. Adenosine receptor subtype expression and activation influence the differentiation of mesenchymal stem cells to osteoblasts and adipocytes. J Bone Miner Res. 2011;26:2112–24.
44. Gharibi B, Abraham AA, Ham J, Evans BA. Contrasting effects of A1 and A2b adenosine receptors on adipogenesis. Int J Obes. 2012;36:397–406.
45. Kaebisch C, Schipper D, Babczyk P, Tobiasch E. The role of purinergic receptors in stem cell differentiation. Comput Struct Biotechnol J. 2015;13:75–84.
46. Katebi M, Soleimani M, Cronstein BN. Adenosine A2A receptors play an active role in mouse bone marrow-derived mesenchymal stem cell development. J Leukoc Biol. 2009;85:438–44.
47. Mediero A, Wilder T, Perez-Aso M, Cronstein BN. Direct or indirect stimulation of adenosine A2A receptors enhances bone regeneration as well as bone morphogenetic protein-2. FASEB J. 2015;29:1577–90.
48. Ciciarello M, Zini R, Rossi L, Salvestrini V, Ferrari D, Manfredini R, et al. Extracellular purines promote the differentiation of human bone marrow-derived mesenchymal stem cells to the osteogenic and adipogenic lineages. Stem Cells Dev. 2013;22:1097–111.
49. Ode A, Schoon J, Kurtz A, Gaetjen M, Ode JE, Geissler S, et al. CD73/5′-ecto-nucleotidase acts as a regulatory factor in osteo−/chondrogenic differentiation of mechanically stimulated mesenchymal stromal cells. Eur Cell Mater. 2013;25:37–47.
50. Napieralski R, Kempkes B, Gutensohn W. Evidence for coordinated induction and repression of ecto-5′-nucleotidase (CD73) and the A2a adenosine receptor in a human B cell line. Biol Chem. 2003;384:483–7.
51. Kara FM, Chitu V, Sloane J, Axelrod M, Fredholm BB, Stanley ER, et al. Adenosine A1 receptors (A1Rs) play a critical role in osteoclast formation and function. FASEB J. 2010;24:2325–33.
52. He W, Wilder T, Cronstein BN. Rolofylline, an adenosine A1 receptor antagonist, inhibits osteoclast differentiation as an inverse agonist. Br J Pharmacol. 2013;170:1167–76.
53. Mediero A, Kara FM, Wilder T, Cronstein BN. Adenosine A(2A) receptor ligation inhibits osteoclast formation. Am J Pathol. 2012;180:775–86.
54. Mediero A, Cronstein BN. Adenosine and bone metabolism. Trends Endocrinol Metab. 2013;24:290–300.
55. Kara FM, Doty SB, Boskey A, Goldring S, Zaidi M, Fredholm BB, et al. Adenosine A(1) receptors regulate bone resorption in mice: adenosine A(1) receptor blockade or deletion increases bone density and prevents ovariectomy-induced bone loss in adenosine A(1) receptor-knockout mice. Arthritis Rheum. 2010;62:534–41.
56. Rossi L, Salvestrini V, Ferrari D, Di Virgilio F, Lemoli RM. The sixth sense: hematopoietic stem cells detect danger through purinergic signaling. Blood. 2012;120:2365–75.
57. Hinton DJ, McGee-Lawrence ME, Lee MR, Kwong HK, Westendorf JJ, Choi DS. Aberrant bone density in aging mice lacking the adenosine transporter ENT1. PLoS One. 2014;9:e88818.
58. Warraich S, Bone DB, Quinonez D, Ii H, Choi DS, Holdsworth DW, et al. Loss of equilibrative nucleoside transporter 1 in mice leads to progressive ectopic mineralization of spinal tissues resembling diffuse idiopathic skeletal hyperostosis in humans. J Bone Miner Res. 2013;28:1135–49.
59. Daniels G, Ballif BA, Helias V, Saison C, Grimsley S, Mannessier L, et al. Lack of the nucleoside transporter ENT1 results in the Augustine-null blood type and ectopic mineralization. Blood. 2015;125:3651–4.
60. Rahman MF, Askwith C, Govindarajan R. Molecular determinants of acidic pH-dependent transport of human equilibrative nucleoside transporter-3. J Biol Chem. 2017;292:14775–85.
61. Campeau PM, Lu JT, Sule G, Jiang MM, Bae Y, Madan S, et al. Whole-exome sequencing identifies mutations in the nucleoside transporter gene SLC29A3 in dysosteosclerosis, a form of osteopetrosis. Hum Mol Genet. 2012;21:4904–9.
62. Listenberger LL, Han X, Lewis SE, Cases S, Farese RV Jr, Ory DS, et al. Triglyceride accumulation protects against fatty acid-induced lipotoxicity. Proc Natl Acad Sci U S A. 2003;100:3077–82.
63. Poloni A, Maurizi G, Serrani F, Mancini S, Zingaretti MC, Frontini A, et al. Molecular and functional characterization of human bone marrow adipocytes. Exp Hematol. 2013;41:558–566 e552.
64. Olmsted-Davis E, Gannon FH, Ozen M, Ittmann MM, Gugala Z, Hipp JA, et al. Hypoxic adipocytes pattern early heterotopic bone formation. Am J Pathol. 2007;170:620–32.

65. Yakar S, Adamo ML. Insulin-like growth factor 1 physiology: lessons from mouse models. Endocrinol Metab Clin N Am. 2012;41:231–47. v
66.•• Rahman S, Lu Y, Czernik PJ, Rosen CJ, Enerback S, Lecka-Czernik B. Inducible brown adipose tissue, or beige fat, is anabolic for the skeleton. Endocrinology. 2013;154:2687–701. **A pioneering study that mechanistically identifies adipogenic signals as osteoanabolic.**
67. Li J, Zhang N, Huang X, Xu J, Fernandes JC, Dai K, et al. Dexamethasone shifts bone marrow stromal cells from osteoblasts to adipocytes by C/EBPalpha promoter methylation. Cell Death Dis. 2013;4:e832.
68. Muthusami S, Ramachandran I, Muthusamy B, Vasudevan G, Prabhu V, Subramaniam V, et al. Ovariectomy induces oxidative stress and impairs bone antioxidant system in adult rats. Clin Chim Acta. 2005;360:81–6.
69. Halade GV, Rahman MM, Williams PJ, Fernandes G. Combination of conjugated linoleic acid with fish oil prevents age-associated bone marrow adiposity in C57Bl/6J mice. J Nutr Biochem. 2011;22:459–69.
70. Hu W, Yu Q, Zhang J, Liu D. Rosiglitazone ameliorates diabetic nephropathy by reducing the expression of chemerin and ChemR23 in the kidney of streptozotocin-induced diabetic rats. Inflammation. 2012;35:1287–93.
71. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev. 2010;31:266–300.
72. Rebiger L, Lenzen S, Mehmeti I. Susceptibility of brown adipocytes to pro-inflammatory cytokine toxicity and reactive oxygen species. Biosci Rep. 2016;36:e00306.
73. Almeida M, Han L, Martin-Millan M, O'Brien CA, Manolagas SC. Oxidative stress antagonizes Wnt signaling in osteoblast precursors by diverting beta-catenin from T cell factor- to forkhead box O-mediated transcription. J Biol Chem. 2007;282:27298–305.
74.• Ambrogini E, Almeida M, Martin-Millan M, Paik JH, Depinho RA, Han L, et al. FoxO-mediated defense against oxidative stress in osteoblasts is indispensable for skeletal homeostasis in mice. Cell Metab. 2010;11:136–46. **This study explains how free radicals generated by aerobic metabolism are handled in osteoblasts to prevent cell death or bone-to-fat switch.**
75. Almeida M, Ambrogini E, Han L, Manolagas SC, Jilka RL. Increased lipid oxidation causes oxidative stress, increased peroxisome proliferator-activated receptor-gamma expression, and diminished pro-osteogenic Wnt signaling in the skeleton. J Biol Chem. 2009;284:27438–48.
76. Grey A, Beckley V, Doyle A, Fenwick S, Horne A, Gamble G, et al. Pioglitazone increases bone marrow fat in type 2 diabetes: results from a randomized controlled trial. Eur J Endocrinol. 2012;166:1087–91.
77. Paccou J, Hardouin P, Cotten A, Penel G, Cortet B. The role of bone marrow fat in skeletal health: usefulness and perspectives for clinicians. J Clin Endocrinol Metab. 2015;100:3613–21.
78. Iwaniec UT, Turner RT. Failure to generate bone marrow adipocytes does not protect mice from ovariectomy-induced osteopenia. Bone. 2013;53:145–53.
79. Justesen J, Mosekilde L, Holmes M, Stenderup K, Gasser J, Mullins JJ, et al. Mice deficient in 11beta-hydroxysteroid dehydrogenase type 1 lack bone marrow adipocytes, but maintain normal bone formation. Endocrinology. 2004;145:1916–25.
80. Ackert-Bicknell CL, Shockley KR, Horton LG, Lecka-Czernik B, Churchill GA, Rosen CJ. Strain-specific effects of rosiglitazone on bone mass, body composition, and serum insulin-like growth factor-I. Endocrinology. 2009;150:1330–40.
81. Fazeli PK, Horowitz MC, MacDougald OA, Scheller EL, Rodeheffer MS, Rosen CJ, et al. Marrow fat and bone–new perspectives. J Clin Endocrinol Metab. 2013;98:935–45.
82. Fazeli PK, Bredella MA, Freedman L, Thomas BJ, Breggia A, Meenaghan E, et al. Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa. J Bone Miner Res. 2012;27:1864–71.
83. Devlin MJ, Cloutier AM, Thomas NA, Panus DA, Lotinun S, Pinz I, et al. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. J Bone Miner Res. 2010;25:2078–88.
84. Menagh PJ, Turner RT, Jump DB, Wong CP, Lowry MB, Yakar S, et al. Growth hormone regulates the balance between bone formation and bone marrow adiposity. J Bone Miner Res. 2010;25:757–68.
85. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18:1319–28.
86. Montagnani A, Gonnelli S. Antidiabetic therapy effects on bone metabolism and fracture risk. Diabetes Obes Metab. 2013;15:784–91.
87. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone. 2014;68:115–23.
88. Schett G, Saag KG, Bijlsma JW. From bone biology to clinical outcome: state of the art and future perspectives. Ann Rheum Dis. 2010;69:1415–9.
89. Yao W, Cheng Z, Busse C, Pham A, Nakamura MC, Lane NE. Glucocorticoid excess in mice results in early activation of osteoclastogenesis and adipogenesis and prolonged suppression of osteogenesis: a longitudinal study of gene expression in bone tissue from glucocorticoid-treated mice. Arthritis Rheum. 2008;58:1674–86.
90. Bernardino JI, Mocroft A, Mallon PW, Wallet C, Gerstoft J, Russell C, et al. Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001/ANRS143 randomised trial. Lancet HIV. 2015;2:e464–73.
91. Grigsby IF, Pham L, Mansky LM, Gopalakrishnan R, Mansky KC. Tenofovir-associated bone density loss. Ther Clin Risk Manag. 2010;6:41–7.
92. Jain RG, Lenhard JM. Select HIV protease inhibitors alter bone and fat metabolism ex vivo. J Biol Chem. 2002;277:19247–50.
93. Xian CJ, Howarth GS, Cool JC, Foster BK. Effects of acute 5-fluorouracil chemotherapy and insulin-like growth factor-I pretreatment on growth plate cartilage and metaphyseal bone in rats. Bone. 2004;35:739–49.
94. Fan C, Georgiou KR, McKinnon RA, Keefe DM, Howe PR, Xian CJ. Combination chemotherapy with cyclophosphamide, epirubicin and 5-fluorouracil causes trabecular bone loss, bone marrow cell depletion and marrow adiposity in female rats. J Bone Miner Metab. 2016;34:277–90.
95. Cromer BA, Scholes D, Berenson A, Cundy T, Clark MK, Kaunitz AM, et al. Depot medroxyprogesterone acetate and bone mineral density in adolescents—the black box warning: a position paper of the Society for Adolescent Medicine. J Adolesc Health. 2006;39:296–301.
96. Hadji P. Aromatase inhibitor-associated bone loss in breast cancer patients is distinct from postmenopausal osteoporosis. Crit Rev Oncol Hematol. 2009;69:73–82.
97. Duque G, Li W, Adams M, Xu S, Phipps R. Effects of risedronate on bone marrow adipocytes in postmenopausal women. Osteoporos Int. 2011;22:1547–53.
98. Wilson C. Bone: risedronate and marrow adiposity. Nat Rev Endocrinol. 2010;6:597.
99. Li GW, Xu Z, Chang SX, Zhou L, Wang XY, Nian H, et al. Influence of early zoledronic acid administration on bone marrow fat in ovariectomized rats. Endocrinology. 2014;155:4731–8.

100. Yang Y, Luo X, Xie X, Yan F, Chen G, Zhao W, et al. Influences of teriparatide administration on marrow fat content in postmenopausal osteopenic women using MR spectroscopy. Climacteric. 2016;19:285–91.
101. Rickard DJ, Wang FL, Rodriguez-Rojas AM, Wu Z, Trice WJ, Hoffman SJ, et al. Intermittent treatment with parathyroid hormone (PTH) as well as a non-peptide small molecule agonist of the PTH1 receptor inhibits adipocyte differentiation in human bone marrow stromal cells. Bone. 2006;39:1361–72.
102. Balani DH, Ono N, Kronenberg HM. Parathyroid hormone regulates fates of murine osteoblast precursors in vivo. J Clin Invest. 2017;127:3327–38.
103. Papapoulos S, Lippuner K, Roux C, Lin CJ, Kendler DL, Lewiecki EM, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM extension study. Osteoporos Int. 2015;26:2773–83.
104. Rosen CJ, Bilezikian JP. Clinical review 123: anabolic therapy for osteoporosis. J Clin Endocrinol Metab. 2001;86:957–64.
105. Cosman F. Anabolic and antiresorptive therapy for osteoporosis: combination and sequential approaches. Curr Osteoporos Rep. 2014;12:385–95.
106. Palacios S, Mejia A. Antiresorptives and anabolic therapy in sequence or combination for postmenopausal osteoporosis. Climacteric. 2015;18:453–5.
107. Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res. 2017;32:198–202.
108. Lou S, Lv H, Wang G, Li Z, Li M, Zhang L, et al. The effect of sequential therapy for postmenopausal women with osteoporosis: a PRISMA-compliant meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016;95:e5496.
109. Song L, Tuan RS. Transdifferentiation potential of human mesenchymal stem cells derived from bone marrow. FASEB J. 2004;18:980–2.