REVIEW ARTICLE

Bone circuitry and interorgan skeletal crosstalk

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Abstract The past decade has seen significant advances in our understanding of skeletal homeostasis and the mechanisms that mediate the loss of bone integrity in disease. Recent breakthroughs have arisen mainly from identifying disease-causing mutations and modeling human bone disease in rodents, in essence, highlighting the integrative nature of skeletal physiology. It has become increasingly clear that bone cells, osteoblasts, osteoclasts, and osteocytes, communicate and regulate the fate of each other through RANK/RANKL/OPG, liver X receptors (LXRs), EphirinB2-EphB4 signaling, sphingolipids, and other membrane-associated proteins, such as semaphorins. Mounting evidence also showed that critical developmental pathways, namely, bone morphogenetic protein (BMP), NOTCH, and WNT, interact each other and play an important role in postnatal bone remodeling. The skeleton communicates not only with closely situated organs, such as bone marrow, muscle, and fat, but also with remote vital organs, such as the kidney, liver, and brain. The metabolic effect of bone-derived osteocalcin highlights a possible role of skeleton in energy homeostasis. Furthermore, studies using genetically modified rodent models disrupting the reciprocal relationship with tropic pituitary hormone and effector hormone have unraveled an independent role of pituitary hormone in skeletal remodeling beyond the role of regulating target endocrine glands. The cytokine-mediated skeletal actions and the evidence of local production of certain pituitary hormones by bone marrow-derived cells displays a unique endocrine-immune-skeletal connection. Here, we discuss recently elucidated mechanisms controlling the remodeling of bone, communication of bone cells with cells of other lineages, crosstalk between bone and vital organs, as well as opportunities for treating diseases of the skeleton.

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Introduction

Bone is a highly organized structure consisting of a protein matrix, primarily type 1 collagen, with hydroxyapatite mineral and cells from different lineages interspersed throughout. Skeletal tissue is composed of two distinct micro-skeletal structures—cortical bone (~80%) and trabecular bone (~20%)—that function as sites of muscle and tendon attachment for locomotion, as major storage sites for calcium, phosphate ions required for intergenerational transfer during procreation, and, as has more recently been established, endocrine organs secreting peptides working on other remote organs.

Bone remodeling, a process in which bone resorption is followed by bone formation in a well-defined spatiotemporal sequence, involves the coordinated activity of osteoclasts and osteoblasts, respectively, both of which differentiate from bone marrow precursors that lie in close proximity

(*Evans, 2007*; *Zaidi, 2007*). Osteoclasts resorb old or damaged bone through the secretion of acid and enzymes that dissolve hydroxyapatite and digest the protein matrix, and their activity is tightly regulated by calcium and hydrogen ion concentrations that they generate locally (*Arnett and Dempster, 1986*; *Zaidi et al., 1989*). The resorptive hemivacuole then fills up with osteoblasts of the mesenchymal stem cell origin, which deposits collagen and non-collagenous proteins and that ultimately undergo mineralization through hydroxyapatite deposition. Osteoblasts that get embedded within the bone matrix become osteocytes, the skeletal equivalent of neurons, which sense and respond to mechanical stresses during terrestrial impact using their intertwined dendritic processes traversing the extensive lacunar network within bone (*Iqbal and Zaidi, 2005*). Osteoblasts, osteoclasts, and osteocytes communicate extensively with each other to couple bone formation and bone resorption. Over the years, it has also become increasingly clear that bone cells in the skeleton intimately interact with immune cells, adipocytes, and hematopoietic cells in the bone marrow, and they are further regulated by the central nervous system, pituitary gland, muscle, and fat.

In all, long-standing efforts to characterize the pathophysiology of aberrant loss or gain of bone in human disease have shed light on novel mechanisms and, importantly, unmasked new actionable targets. Below, we will discuss cellular crosstalk between bone cells, as well as the communication between the skeleton and other organ systems, namely, immune, nervous, neuroendocrine, and other major organs to highlight the therapeutic applications of integrative bone physiology.

Osteoblast and osteoclast activities are coupled in space and time

Insights into the coupling of bone resorption and bone formation have come to light with the realization that transforming growth factor (TGF) β1 is a central player. TGFβ1, released from bone matrix during resorption, is the primary inducer of bone marrow-derived mesenchymal stem/stromal cell (BMSC) migration to the resorptive hemivacuole as well as their spatial localization (*Iqbal et al., 2009*; *Tang et al., 2009*). Disrupting the TGFβ1 gradient in mice with an activating *Tgfb1* mutation recapitulates Camurati-Engelmann disease, characterized by disorganized stromal cell recruitment, dysplastic bones, and increased risk of fracture (*Tang et al., 2009*).

Parathyroid hormone (PTH) action on the skeleton represents a classical example of osteoblast-osteoclast coupling. Increased osteoclastic bone resorption from continuous PTH exposure is mediated through PTH receptor activation in osteoblasts, not osteoclasts (*McSheehy and Chambers, 1986*). The activated PTH/PTH receptor stimulates the secretion of receptor activator of nuclear factor kappa-Β ligand (RANKL), a member of the tumor necrosis factor alpha (TNFα) family that binds to RANK on osteoclast precursors to induce osteoclastic differentiation (*Hsu et al., 1999*; *Huang et al., 2004*; *Lacey et al., 1998*; *Simonet et al., 1997*). RANKL is also secreted by osteocytes, and the osteocyte-selective deletion of *Rankl* results in lower number of osteoclasts, highlighting the role of the osteocyte as a mechanosensor that coordinates site-specific osteoclast recruitment and bone resorption (*Nakashima et al., 2011*; *Xiong et al., 2011*; *Xiong et al., 2015*). Another key player in RANK-RANKL axis that couples osteoblastic activation with osteoclastic resorption is osteoprotegerin (OPG), again secreted by osteoblasts, which serves as a decoy receptor to RANKL and regulates RANK/RANKL binding ratio, and consequently, the rate of osteoclasts differentiation and action (*Simonet et al., 1997*; *Figure 1*).

The recent identification of liver X receptors (LXRs) has provided further insight into the endogenous mechanism that determines the RANKL/OPG equilibrium within osteoblasts (*Kleyer et al., 2012*). The two types of LXRs, α and β, have been known to regulate cholesterol metabolism and the immune response (*Zelcer and Tontonoz, 2006*). However, in co-cultures of osteoblasts and osteoclasts, LXR ligand treatment decreased the RANKL/OPG ratio and interfered with osteoblast-induced osteoclastogenesis. This in vitro finding was supported by an ovariectomized rodent model in which LXR agonist administration attenuated osteoclast differentiation and rescued ovariectomy-induced bone loss (*Kleyer et al., 2012*). In this context, leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4) also regulates osteoclast differentiation. LGR4, expressed in osteoclasts, binds RANKL and prevents the nuclear translocation of nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent 1 (NFATc1), preventing osteoclastogenic gene expression. Moreover, activated

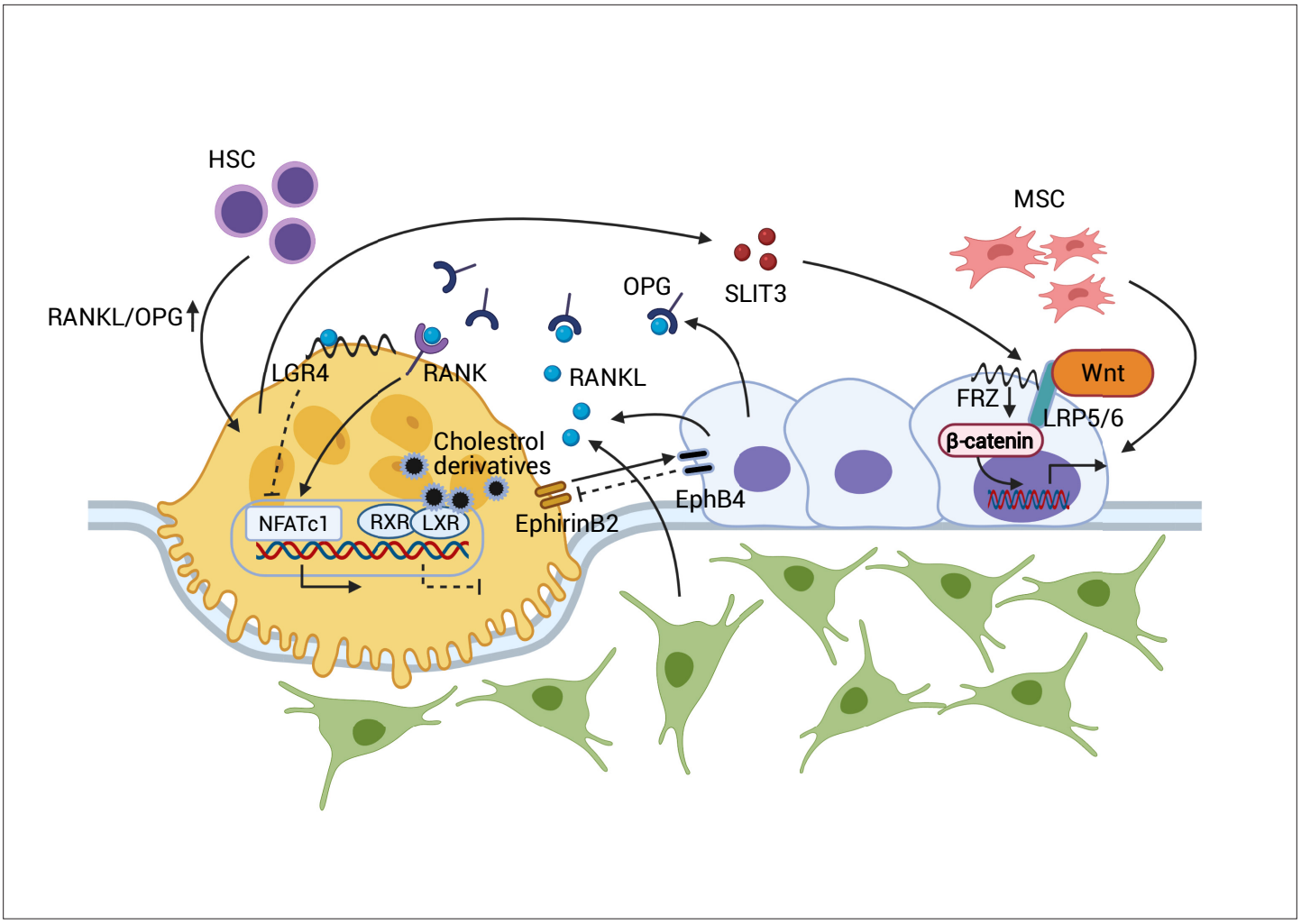

Figure 1. Coupling between osteoblasts and osteoclasts. RANKL/OPG regulates osteoclastogenesis through RANK and downstream NFATc1 activation. RANKL-LGR4 binding creates a negative feedback loop by inhibiting NFATc1. LXR-RXR suppresses osteoclastogenesis upon binding of cellular cholesterol derivatives. EphB4-EphrinB2 interaction promotes osteoblastogenesis and suppresses osteoclastogenesis. SLIT3 from osteoclasts activates WNT/β-catenin and stimulates osteoblast migration and proliferation. Abbreviations: Hematopoietic stem cell (HSC); mesenchymal stem cell (MSC); receptor activator of nuclear factor kappa- B (RANK); receptor activator of nuclear factor kappa- B ligand (RANKL); leucine-rich repeat-containing G protein-coupled receptor 4 (LGR4); liver X receptors (LXRs); retinoic acid receptor (RXR); nuclear translocation of nuclear factor of activated T cells cytoplasmic, calcineurin-dependent 1 (NFATc1); slit guidance ligand 3 (SLIT3); osteoprotegerin (OPG); frizzled (Frz).

NFATc1 induces transcription of *Lgr4* in osteoclasts, negatively regulating RANK/RANKL-induced osteoclastogenesis (***Luo et al., 2016***; ***Zaidi and Iqbal, 2016***; ***Figure 1***).

Osteoblast-osteoclasts coupling is in fact bidirectional in that osteoclasts also affect osteoblast formation and function. EphrinB2, a transmembrane protein expressed by osteoclasts, interacts with its receptor, EphB4, on osteoblasts. EphirinB2-EphB4 signaling in osteoclasts suppresses osteoclastogenesis by inhibiting the c-Fos-NFATc1 signal, whereas in osteoblasts, it upregulates osteogenic genes, such as *Osx* and *Runx2*, and promotes bone formation (***Zhao et al., 2006***). Further, the osteoclast-secreted axon guidance molecule, SLIT3, stimulates osteoblast migration and proliferation by activating β-catenin. Osteoclast-specific *Slit3*-deficient mice thus demonstrate reduced bone mass, whereas osteoblast-specific *Slit3* deletion results in normal bone mass (***Kim et al., 2018***; ***Figure 1***).

Sphingolipids and other membrane-associated proteins also facilitate synchronous osteoblast-osteoclast coupling. Sphingosine-1-phosphate, a signaling sphingolipid, controls both osteoblastic bone formation and osteoclast precursor migration during bone remodeling. It also functions as a chemoattractant, directing osteoclast precursors to sites of stress (***Ishii et al., 2009***; ***Pederson et al., 2008***). Likewise, semaphorins, a class of membrane-associated secreted proteins, either enhance or

suppress bone formation. Semaphorin 3A (*Sema3A*)-deficient mice receiving recombinant Sema3A display a rescue of osteoblastic bone formation and osteoclastic bone resorption (**Hayashi et al., 2012**; **Zaidi and Iqbal, 2012**). Osteoclast-derived Sema4D, however, suppresses bone formation when it binds to its osteoblast receptor Plexin-B1 (**Negishi-Koga et al., 2011**).

In all, understanding the coupling of bone cells has prompted new treatments for bone diseases, such as osteoporosis, and continue to offer potential therapeutic targets. A monoclonal antibody against RANKL, denosumab, is currently popular for treating both osteoporosis and skeletal metastasis (**McClung et al., 2006**). Given that targeting LGR4 only affects mature osteoclasts and not precursor cells, there is a potential in using its extracellular domain as a means of binding excess RANKL to restrict bone resorption (**Luo et al., 2016**; **Zaidi and Iqbal, 2016**). Furthermore, enhancing EphrinB2-EphB4 or inhibiting Sema4D holds therapeutic promise to promote bone formation.

Developmental genes reawaken during adult bone remodeling

Three critical developmental pathways, namely bone morphogenetic protein (BMP), NOTCH, and WNT signaling pathways, remain active beyond morphogenesis to regulate adult bone remodeling. They interact with the master transcriptional regulators RUNX2, Osterix (OSX), activating transcription factor 4 (ATF4), and Schnurri-2. Other developmental genes that promote pluripotency, such as octamer-binding transcription factor 4 (*Oct4*) and sex-determining region Y-box 2, are also expressed in mesenchymal stem cells during osteogenic differentiation (**Matic et al., 2016a**). However, it has been proven conclusively that *Oct4* has no role in bone homeostasis.

A fundamental role for members of the BMP family in skeletal development and remodeling is well documented. Osteoblasts and osteoclasts express multiple BMPs, namely (BMP-2, -4, -5, -7, and -9) and the BMP receptors (BMPRs), type I and II (**Huntley et al., 2019**; **Wu et al., 2016**). Intracellular BMP signaling is mediated by SMAD-dependent and non-SMAD-dependent pathways. BMP/BMPR binding phosphorylates the BMP-specific receptor-regulated SMADs, SMAD-1, -5, and -8 to form a heterodimeric SMAD-1/5/8 complex that translocates to the nucleus with SMAD-4. In the non-SMAD-dependent pathway, BMP/BMPR binding phosphorylates TGFβ-activated kinase (TAK1) and activates the JNK and p38 MAPK signaling pathways. Both pathways then increase the transcriptional activity of *Runx2*, *Dlx5*, and *Osx* (**Wan and Cao, 2005**; **Wu et al., 2016**). The BMP signaling pathway is regulated at many levels. Noggin (NOG), a glycoprotein secreted by osteoblasts, binds BMPs selectively and competitively inhibits BMP action on the cell surface. Osteoblast-specific *Nog* overexpression in mice shows decreased trabecular bone volume and impaired osteoblast function with increased fractures (**Devlin et al., 2003**). NOG levels in mice appear to increase with aging, which might contribute to age-related low bone turnover (**Wu et al., 2003**). Inhibitory SMAD proteins, such as SMAD-6 and -7, prevent downstream phosphorylation of the SMAD-1/5/8 complex. The BMP pathway is also regulated by the ubiquitin-proteasome system. For example, the SMAD-specific E3 ubiquitin protein ligase (Smurf)-1 downregulates BMP signaling in osteoblasts by promoting SMAD-1 degradation (**Zhao et al., 2004**; **Zhu et al., 1999**). Smurf1 also mediates TNF-induced suppression in osteoblastogenesis through its interaction with SMAD-6 and RUNX2 downregulation (**Kaneki et al., 2006**; **Shen et al., 2006**). Lastly, the ubiquitin-conjugating enzyme 9 targets SMAD-4 for degradation to suppress BMP pathway signaling (**Wan and Cao, 2005**).

The NOTCH receptor, a single transmembrane domain receptor protein required for somite maturation, is another critical developmental molecule that also regulates postnatal skeletal homeostasis. The binding of its ligands, JAGGED-1 and -2 and delta-like ligand 1–3, results in the cleavage of the NOTCH intracellular domain (NICD) by γ-secretases presenilin-1 and -2 (**Bassett et al., 2008**). The cleaved, active NICD undergoes nuclear translocation and interacts with CSL (CBF1, suppressor of hairless, lag-1) transcription factors to activate target gene expression (**Luo et al., 2019**). NOTCH signaling triggers proliferation and maintains a pool of osteoblast progenitors, while repressing differentiation of early osteoblasts to terminally differentiated cells (**Engin et al., 2008**; **Hilton et al., 2008**). Up- or downregulated NOTCH signaling yields distinct skeletal phenotypes depending on the stage of osteoblast lineage differentiation. Mice that overexpress *Notch1* driven by an early promoter Col3.6 repress osteoblast differentiation and develop osteopenia (**Zanotti et al., 2008**). Similarly, patients with Hajdu-Cheney syndrome, a rare genetic disease characterized by significant bone loss

and fractures, have gain-of-function *NOTCH2* mutations. This condition was recapitulated in mice with a *Notch2*^{Q2319X} mutation, exhibiting osteopenia with excessive bone remodeling (**Canalis et al., 2016**). Conversely, when NOTCH ligand JAGGED-1 was deleted in osteoprogenitor cells, increased trabecular bone mass with increased osteoblast activity was noted (**Lawal et al., 2017**). Likewise, the loss of γ-secretases presenilin-1 and -2 in osteoblast progenitors yielded a high bone mass phenotype at an early age, but the mice progressively lost bone with aging (**Engin et al., 2008**)—together suggesting that a NOTCH-mediated regulatory loop maintains the population of osteolineage cells.

The WNT signaling pathway is integral to the developmental patterning of the dorsal somite and, being ubiquitously expressed, regulates cell growth and differentiation (**Fuentealba et al., 2007**). Canonical WNT signaling is initiated upon simultaneous binding of WNT ligands to the frizzled (FRZ) and low-density lipoprotein receptor-related protein (LRP) 5/6 receptors. Activation of the co-receptors leads to the inhibition of glycogen synthase kinase 3 activity and stabilization of β-catenin. The stabilized β-catenin subsequently undergoes nuclear translocation and interacts with the transcription factors T-cell factor and lymphoid enhancer factor to promote osteoblast gene expression (**MacDonald et al., 2009**). The β-catenin-mediated canonical pathway interacts with the BMP pathway through Axin-related protein (Axin)2, which promotes β-catenin degradation. Axin2-deficient mice display increased bone mass; this anabolic effect is dependent on BMP-2/4 and OSX (**Yan et al., 2009**).

Murine genome-wide association studies (GWAS) and the identification of WNT gene variants with significant skeletal phenotype, notably *LRP5* mutations causing osteoporosis-pseudoglioma syndrome and *SOST* mutations leading to sclerosteosis and Van Buchem disease, have together established WNT signaling as a cornerstone of skeletal homeostasis (**Boyden et al., 2002**; **Krishnan et al., 2006**; **Rivadeneira et al., 2009**). Mechanistically, WNT/β-catenin activation in adult mice increases bone mass by enhancing stem cell renewal, pre-osteoblast proliferation, and osteoblast differentiation, while inhibiting osteoblast and osteocyte apoptosis (**Baliram et al., 2011**; **Krishnan et al., 2006**; **Zhang et al., 2013**). The downstream effects of WNT signaling, along with β-catenin-mediated osteoclast inhibition, have led to the recent development of an anti-osteoporosis drug with dual pro-anabolic and anti-resorptive actions. Romosozumab, a monoclonal antibody against the bone-specific WNT inhibitor sclerostin, now FDA-approved, has shown promising efficacy in reducing vertebral, non-vertebral, and hip fractures (**Cosman et al., 2016**; **Saag et al., 2017**). Dickkopf-1 (DKK1), another WNT inhibitor, contributes to myeloma-related bone disease as the production of DKK1 by myeloma cells increases the RANKL/OPG ratio (**Qiang et al., 2008**). An anti-DKK1 monoclonal antibody is now being studied for use as a potential therapeutic agent (**Fulciniti et al., 2009**).

Chatter between bone and immune cells in bone marrow

The physical proximity of bone and bone marrow allows close interactions between bone cells and bone marrow-derived cells. Osteoclasts, derived from hematopoietic stem cells (HSCs), bear the immune receptor osteoclast-associated receptor (OSCAR) to activate receptor expressed on myeloid cells (TREM) 2, signal-regulator protein beta (SIRPβ) 1, and paired immunoglobulin-like receptor A (PIRA), establishing the physiologic relevance of the osteo-immune interface (**Barrow et al., 2011**; **Otero et al., 2012**; **Pfeilschifter et al., 1989**; **Takayanagi, 2007**). The RANK-RANKL interaction is mediated through the recruitment of TNF receptor-associated factor 6 and, at the same time, the phosphorylation of immune-receptor tyrosine-based activation motifs (ITAMs), such as DAP12 and Fc receptor subunit, resulting in NF-κB activation and cytosolic Ca^{2+} release. NFATc1 is then activated by calcineurin and amplified in cooperation with activator protein 1 (**Asagiri et al., 2005**). Consequently, gain-of-function mutations of calcineurin result in markedly increased NFATc1 and osteoclast differentiation, whereas its downregulation suppresses osteoclast formation (**Sun et al., 2007**). Calcineurin inhibitors like tacrolimus, a commonly used immunosuppressant, can cause low bone turnover and reduced bone formation (**Epstein et al., 2003**; **Sun et al., 2005**). *CanA*-deficient mice showed markedly reduced mineral apposition rates with osteogenic genes downregulation, namely, *Runx2*, *Bsp,* and *Ocn* (**Sun et al., 2005**). In contrast, ITAM-deficient mice (*Dap12*$^{-/-}$*FcRγ*$^{-/-}$*) preserve bone mass after ovariectomy* (**Wu et al., 2007**).

Other immune cells in the bone marrow produce several pro- and anti-osteoclastogenic cytokines that together optimize overall osteoclast differentiation. While TNFα stimulates osteoclastogenesis, IFNγ and interferon regulating factor 8 (IRF8) suppress osteoclast formation. *Irf8*-deficient mice thus

show significant osteoporosis due to increased osteoclastogenesis (**Zhao et al., 2009**). Furthermore, T-helper 17 (Th17) cells secrete predominantly RANKL and TNF (compared with IFNγ), which support its contribution to hyper-resorption in autoimmune arthritis (**Komatsu et al., 2014**). Th17 cells secrete IL-17A, which is required for PTH to exert its catabolic effects on bone (**Li et al., 2015**). This is, in part, through the indirect stimulation of RANKL production by osteocytes through IL-17A signaling (**Li et al., 2019**). Taken together, it is clear that bone and bone marrow-derived cells interact closely to maintain skeletal homeostasis with the immune system serving as a bridge.

Osteogenesis, hematopoiesis, and angiogenesis in local partnership

Findings over the past decade have established that bone remodeling and blood formation are critically entwined, with the osteoblast playing a central role in the regulation of hematopoiesis. The regulatory microenvironment, or the so-called 'niche' where HSCs reside, also involves BMSCs and osteoblasts (**Méndez-Ferrer et al., 2010**). Spindle-shaped N-cadherin+ CD45 osteoblastic cells and angiopoietin-1-expressing osteoblasts have been shown to protect and maintain HSCs in the niche (**Arai et al., 2004**; **Zhang et al., 2003**). Through WNT and NOTCH signaling, they promote HSC renewal, maturation, and survival in response to PTH (**Calvi et al., 2003**; **Fleming et al., 2008**; **Weber and Calvi, 2010**). Other transcriptional factors, like growth factor independence 1b, are also involved in maintaining HSC cellularity and functional integrity through the regulation of WNT signaling (**Shooshtarizadeh et al., 2019**). This interaction of bone marrow with bone is, in part, mediated by the sympathetic nervous system (SNS). CXCL12, a chemokine that directly causes HSC migration, is regulated by circadian secretion of noradrenaline by sympathetic nerves innervating BMSCs through β-adrenergic receptors (**Katayama et al., 2006**; **Méndez-Ferrer et al., 2008**). Thus, disrupting sympathetic signal interferes with HSC maintenance. For example, acute myelogenous leukemia-induced sympathetic neuropathy commits mesenchymal progenitors to the osteoblast lineage at the expense of HSC-maintaining periarteriolar niche cells (**Hanoun et al., 2014**).

In addition to regulating hematopoiesis, osteoblasts also regulate erythropoiesis by producing erythropoietin (EPO) in response to hypoxia. This increased EPO production is caused by enhanced hypoxia-inducible factor-alpha (HIF-α) signaling in osteoblastic precursors within the niche, resulting in selective expansion of the erythroid lineage (**Rankin et al., 2012**). Increased EPO and abnormal erythroid proliferation are proposed mechanism of low bone mass in patients with ineffective erythropoiesis such as β-thalassemia. Iron metabolism also plays a significant role in bone remodeling through action of erythroferrone (ERFE), a protein secreted by erythroblasts in bone marrow, a negative regulator of hepcidin. ERFE was shown to bind to BMP family-2, -6, and -2/6 heterodimer (**Castro-Mollo et al., 2021**; **Wang et al., 2020**). By using *Erfe*$^{-/-}$ mice and β-thalassemic mice with systemic loss of ERFE expression (*Hbb*$^{th3/+}$;*Erfe*$^{-/-}$), our group showed that ERFE was highly expressed in osteoblasts even compared with erythroblasts, and the absence of ERFE caused high bone turnover and significant bone loss. By suppressing bone turnover from downregulating BMP-2-mediated signaling and RANKL production, ERFE was shown to exert bone protective effects (**Castro-Mollo et al., 2021**).

Augmented HIF-α activity enhances angiogenesis and osteogenesis (**Schipani et al., 2009**; **Wang et al., 2007**; **Wu et al., 2015**). Increased *Hifα* expression results in proliferation of a specific subpopulation of endothelial cells (Type H), especially in the metaphysis of long bones, and increases the survival and proliferation of osteoprogenitors (**Wang et al., 2007**). The coupling of angiogenesis and osteogenesis is further highlighted by the dual role of vascular endothelial growth factor (VEGF)-A. VEGF not only promotes endothelial cell migration and proliferation, but also stimulates osteogenesis through the positive regulation of osteogenic growth factors (**Schipani et al., 2009**). Molecular crosstalk through angiocrine-, NOTCH-, and NOG-related signals also links angiogenesis and osteogenesis (**Kusumbe et al., 2014**). Defective angiocrine release of NOG, promoted by NOTCH, results in skeletal defects and impaired angiogenesis (**Kusumbe et al., 2014**). The effects of these signaling pathways are mediated by a subtype of vessels, called CD31^{hi}/Emcn^{hi}, which generates a distinct TGFβ3-rich microenvironment to maintain perivascular osteoprogenitors (**Kusumbe et al., 2014**). All of this together supports the fact that osteogenesis and angiogenesis are coupled tightly, new information that is especially critical in relation to fracture healing (**Schipani et al., 2009**; **Wang et al., 2007**).

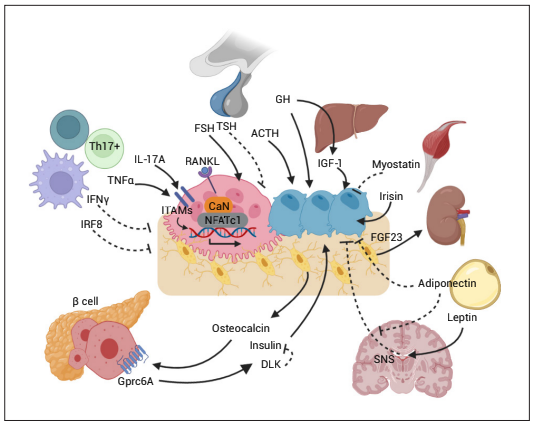

Figure 2. Skeletal crosstalk with other organs. Pituitary hormones directly regulate bone remodeling. FSH stimulates osteoclastogenesis, whereas TSH inhibits osteoclastic bone resorption. ACTH promotes osteoblastic bone formation. GH triggers anabolic signals directly and indirectly through IGF-1. Leptin-mediated SNS activation negatively regulates bone remodeling. The inhibitory peripheral action of adiponectin on bone opposes its centrally mediated action by blocking SNS. OCN, upon binding to the GPRc6A receptor on pancreatic β-cells, can enhance β-cell proliferation and insulin secretion. Insulin binding on osteoblasts can, in turn, promote OCN production. DLK from β-cells counteracts OCN activity by inhibiting the stimulatory effect of insulin. Osteocytes release FGF23, which promotes renal phosphate excretion. Myokines, such as myostatin and irisin, also directly affect bone remodeling. Immune-bone interactions notably occur through various cytokines, such as TNFα, IL-17A, IFNγ, and IRF8. Abbreviations: Follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), growth hormone (GH), adrenocorticotropic hormone (ACTH), receptor activator of nuclear factor kappa- B (RANK), sympathetic nervous system (SNS), delta-like protein (DLK), interferon regulatory factor 8 (IRF8), interferon (IFN), tumor necrosis factor (TNF), interleukin (IL), immunoreceptor tyrosine-based activation motif (ITAM), calcineurin (CaN), G protein-coupled receptor class C group 6 member A (GPRC6A), osteocalcin (OCN), fibroblast growth factor (FGF).

Pituitary hormones expand their circuitry

The pituitary gland largely orchestrates peripheral hormone secretion from various endocrine organs in response to hypothalamic signals. Beyond their traditional roles, now we know that pituitary hormones also have direct effects on skeleton remodeling (***Figure 2***). Both osteoclasts and osteoblasts express G protein-coupled receptors (GPCRs) for thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), growth hormone (GH), adrenocorticotropic hormone (ACTH), prolactin (PRL), oxytocin (OXT), and vasopressin (AVP) (***Abe et al., 2003***; ***Fritton et al., 2010***; ***Seriwatanachai et al., 2008***; ***Sun et al., 2006***; ***Tamma et al., 2009***; ***Tamma et al., 2013***; ***Zaidi et al., 2010***).

It is challenging to examine an independent skeletal effect of pituitary hormones due to reciprocal relationship between the pituitary and the endocrine targets. Abe et al. first described an independent effect of TSH signaling using haploinsufficient TSH receptor mice (*Tshr*$^{+/-}$) that had normally developed thyroid follicles and normal thyroid function (***Abe et al., 2003***). Furthermore, induction of an iatrogenic hyperthyroid state in mice supplementing T4 caused profoundly higher bone loss in mice without the TSHR compared with wild type mice (***Baliram et al., 2012***). This preclinical data is consistent with strong negative correlations between low serum TSH levels and bone turnover markers, bone mineral density and fracture risk from several population-based observational studies (***Aubert et al., 2017***; ***Kim et al., 2006***; ***Kim et al., 2021***; ***Morris, 2007***).

The skeletal effect of TSH, at least in part, is mediated through bone-active cytokines. TNFα was upregulated In *Tshr*$^{-/-}$ mice, with RANK-L and M-CSF being unchanged (***Abe et al., 2003***). Compound mutants of TSHR and TNFα deficiency confirmed that TNFα plays a critical role in bone loss and increased osteoclastogenesis in the absence of TSH signaling (***Hase et al., 2006***; ***Sun et al., 2013***). This is another fascinating example of interaction between endocrine and immune cells on skeletal remodeling (see above). However, the effect of TSH on osteoblasts seems not as straightforward. Our initial description of an anti-osteoblastic effect of TSH in vitro through the downregulation of VEGF receptor (FLK-1) and the WNT co-receptor, LRP5 (***Abe et al., 2003***), was followed by our intervention study using recombinant human TSH (rhTSH)—this showed clear evidence of an anabolic action in vivo. Intermittent administration of small dose of rhTSH increased osteoblastogenesis and bone mass, without altering thyroid hormones (***Sampath et al., 2007***; ***Sun et al., 2008***). A direct anabolic effect of rhTSH in terms of inducing an elevation in the bone formation marker procollagen 1 intact N-terminal pro-peptide was also established in people (***Martini et al., 2008***). Furthermore, subjects with the gain-of-function polymorphism (*TSHR*^{D727E}) displayed higher bone mass (***Heemstra et al., 2008***; ***van der Deure et al., 2008***). Recent findings suggest that TSH-induced osteoblastic action might be mediated by β-arrestin,

which serves as a scaffold linking GPCRs to Erk1/2 signaling. TSH-induced binding of β-arrestin-1 to TSHR, which then phosphorylated Akt1, p38, and Erk1/2 and, by doing so, upregulated *Alp*, *Rankl*, and *Opn*. Knockdown of β-arrestin-1 inhibited TSHR-mediated osteogenic gene upregulation (**Boutin et al., 2020**; **Cassier et al., 2017**; **Ramajayam et al., 2012**). In all, these studies are meaningful clinically, in that they could explain the bone loss in patients with subclinical hyperthyroidism, where TSH levels are low and serum thyroid hormones are relatively normal. With that said, it also seems clear that it may be unnecessary to over-suppress serum TSH in patients other than in patients with thyroid cancer, where such suppression is clinically necessary. In that situation, an anti-resorptive therapy may be mandated to prevent bone loss.

In 2006, we reported for the first time that FSH also directly regulates bone remodeling. It acts on FSH receptors (FSHRs) coupled to the G protein, $G_{i2\alpha}$, to increase osteoclastic bone resorption and suppress bone formation (**Robinson et al., 2010**; **Sun et al., 2006**; **Sun et al., 2007**; **Zhu et al., 2012b**). FSH also enhances RANK and, by doing so, indirectly promotes osteoclastogenesis by stimulating the release or altering the receptor expression of TNFα, IL-1β, and IL-6 (**Cannon et al., 2010**; **Cannon et al., 2011**; **Iqbal et al., 2006**; **Wang et al., 2015**).

Haploinsufficient FSHR mice (*Fshr*$^{+/-}$) had normal estrogen levels and developed an intact uterus; yet they showed higher bone mass compared with wild type mice (**Sun et al., 2006**). A separate study also showed higher bone volume and less trabecular spacing in the absence of Fshβ (**Morgan et al., 2022**). In addition, administering recombinant FSHβ augmented ovariectomy-induced bone loss, while blocking with anti-FSHβ antibody reversed the ovariectomized bone loss (**Liu et al., 2010**; **Zhu et al., 2012b**). These findings are underscored by findings from human observational studies using large epidemiologic cohorts of different ethnicity, namely the Study of Women's Health Across the Nation (SWAN), AGES-Reykjavik Study of Older Adults and Chinese cohorts, all of which noted a strong inverse correlation between serum FSH levels and bone mass independently of estrogen levels (**Adami et al., 2008**; **Cheung et al., 2011**; **Gallagher et al., 2010**; **Randolph et al., 2003**; **Sowers et al., 2003**; **Veldhuis-Vlug et al., 2021**; **Wu et al., 2010**; **Xu et al., 2009**). Moreover, women with an activating *FSHR* polymorphism (rs6166) display a lower bone mass and high resorption markers (**Rendina et al., 2010**).

Taken together, it is plausible that elevated FSH levels, which precede estrogen deficiency during the menopausal transition, contribute to the rapid bone loss that begins during the late perimenopause. Noting the therapeutic relevance of these findings in relation to results from SWAN, we developed a humanized, epitope-specific FSH-blocking antibody as a potential therapeutic for osteoporosis (**Gera et al., 2020**). Interestingly, we also showed that blocking FSH reduces body fat, increases energy expenditure, and prevents neurodegeneration in mouse models. It is possible therefore that FSH blockade in the early years of the menopause may, in fact, reduce the extent of bone loss, visceral obesity, energy dysregulation, and the spikes of cognitive decline that are noted as early as the late perimenopause, when, as stated above, serum FSH levels are rising in the face of normal estrogen as a response to declining ovarian reserve.

GH is, expectedly, an important hormone as a growth signal that mediates postnatal longitudinal bone growth. It is now clear that GH not only works through IGF-1, but also acts directly on the skeleton (**Bouillon, 1991**). GH receptor-deficient and IGF-1-deficient mice both showed a similar ~25–30% reduction in body length compared to wild type mice with a significant further reduction in mutant mice lacking both molecules (**Lupu et al., 2001**). Furthermore, peripheral GH administration enhanced cartilage growth in hypophysectomized and GH-deficient rodents (**Isaksson et al., 1987**; **Isaksson et al., 1991**; **Ohlsson et al., 1998**) and reversed the osteopenic phenotype of estrogen-deficient and liver-derived IGF-1-deficient mice (**Fritton et al., 2010**)—altogether suggesting a direct local skeletal effect of GH.

The systemic and local effects of IGF-1 on the skeleton have been carefully examined using genetically modified mice. Liver-specific IGF-1-deficient mice, which displayed decreased circulating IGF-1 (by ~75%), surprisingly showed normal skeletal growth with *albeit* impaired cortical bone parameters (**Sjögren et al., 1999**; **Yakar et al., 1999**). However, bone-specific IGF-1-deficient mice showed significantly reduced bone size and bone mass, impaired bone formation and mineralization, despite normal levels of circulating IGF-1 (**Govoni et al., 2007**). This indicates a critical role for locally produced IGF in skeletal regulation. A certain level of systemic IGF-1 is still required for skeletal growth. Systemic IGF-1 deletion caused greater bone loss compared with bone-specific IGF-1 deletion, and the re-expression

of liver-specific IGF1 in global IGF-1-deficient mice achieved ~30% of postnatal growth (***Stratikopoulos et al., 2008***). In addition, a further decrement of IGF-1 below ~10% in liver-specific IGF-1-deficient mice by deleting IGF-binding protein-3 and the acid labile subunit resulted in marked growth retardation (***Ohlsson et al., 2009***; ***Yakar et al., 2009***). Together, these findings suggest that GH, systemic IGF-1, and local IGF-1 exert a direct effect on postnatal skeletal growth.

We found that ACTH was also directly involved in bone remodeling by bypassing known glucocorticoid-mediated action. ACTH enhances osteoblastic differentiation by upregulating the protease inhibitor alpha-2-macroglobulin, which likely promotes osteoblastic differentiation through TGFβ induction (***Sadeghi et al., 2020***). It also increases VEGF expression through the melanocortin receptor MC2R on osteoblasts (***Zaidi et al., 2010***). Given the pathophysiologic role of vascular insufficiency due to VEGF suppression in avascular necrosis (AVN) of the femur, ACTH can be a therapeutic target for treating AVN of the femur (***Kerachian et al., 2010***; ***Sadeghi et al., 2020***).

Other pituitary hormones like PRL and OXT are also implicated in calcium homeostasis and bone remodeling. Pregnancy and lactation are characterized by excessive maternal bone resorption and bone loss, both of which are reversed upon weaning (***Sowers et al., 1995***; ***Wysolmerski, 2002***). PRL inhibits bone formation and stimulates bone resorption by suppressing OPG (***Coss et al., 2000***; ***Seriwatanachai et al., 2008***). During pregnancy, OXT appears to facilitate maternal skeletal mobilization for fetal bone ossification through increased osteoclastic resorption and suppressed bone formation (***Liu et al., 2009***). Genetically modified *Oxt*- and *Oxtr*-deficient mice displayed severe age-related bone loss due mainly to a bone-forming defect (***Tamma et al., 2009***). Consistent with this, osteoblast- and osteoclast-specific deletion of *Oxtr*s showed low and high bone mass, respectively (***Sun et al., 2019***).

Vasopressin, a key regulator of serum osmolality and fluid status, has also been implicated in bone remodeling. In contrast to Oxtr-deficient mice, *Avpr*-null mice displayed a high bone mass phenotype arising from increased bone formation and reduced bone resorption, indicating that vasopressin negatively regulates skeletal remodeling (***Sun et al., 2016***; ***Tamma et al., 2013***). This finding might explain the profound bone loss in patients with chronic hyponatremia, which is often accompanied by high vasopressin levels (***Tamma et al., 2013***).

Lastly, and importantly, there is emerging evidence that certain pituitary hormones are produced locally by bone marrow-derived cells and regulate bone remodeling in a paracrine manner. ACTH is produced by macrophages (***Pállinger and Csaba, 2008***), suggesting that MC2R in bone may be regulated locally in addition to its systemic control. Macrophage and CD11β^{+} cells also express a splice variant of TSH, TSHβv, which is biologically active and confers an osteoprotective effect (***Baliram et al., 2013***; ***Baliram et al., 2016***). In all, therefore, new pituitary-bone circuitry of biologic and medical importance continues to evolve through the use of genetically mouse models. This provides the framework for the extension of such circuitry in the regulation of other somatic and central functions, such as body fat regulation, energy metabolism, inflammation, and central neural functions, by pituitary hormones—a new physiology that is just beginning to be unearthed.

Two-way traffic between bone and brain

A brain-bone connection has been evident from multiple human and mouse studies. Early studies established the SNS as a negative regulator of bone formation through the action of the adipokine, leptin, and the hypothalamic leptin receptor (LEPR) (***Yamashita et al., 1998***; ***Figure 2***). Intracerebroventricular leptin administration reduced bone mass and bone formation (***Ducy et al., 2000***), actions that were mediated by osteoblastic β2-adrenergic receptors (Adrb2) (***Takeda et al., 2002***). The therapeutic potential of non-selective β-adrenergic antagonists, like propranolol, in bone mass regulation in people has also been confirmed (***Reid et al., 2005***; ***Schlienger et al., 2004***; ***Takeda et al., 2002***). In contrast, the osteoclastic effect of leptin is facilitated by two distinct, antagonistic pathways. Leptin-mediated SNS activation promotes osteoclastogenesis through increased RANKL expression, which is counteracted by increased secretion of the neuropeptide CART by the hypothalamus secondary to leptin-LEPR binding (***Elefteriou et al., 2005***).

At the level of sympathetic ganglia, leptin-enhanced sympathetic outflow is initiated by the transcription factor FOXO1, which in turn increases the expression of dopamine β-hydroxylase (***Kajimura et al., 2014***). The upregulation of molecular clock genes, namely *Per* and *Cry*, downstream of Adrb2 activation promotes osteoblast proliferation through upregulation of *c-fos* and *Jun* (***Fu et al., 2005***).

These findings suggest that the process of bone remodeling relies on oscillations of gene expression or circadian rhythmicity (**Fu et al., 2005**). Of note, parasympathetic nerve terminals originating from the spinal cord release acetylcholine (ACh) to interact with nicotinic ACh receptors and antagonize SNS tone, thus inhibiting bone resorption and increasing bone mass (**Bajayo et al., 2012**). Central parasympathetic regulation is mediated by IL-1 (**Bajayo et al., 2012**; **Bajayo et al., 2005**).

In addition to SNS and parasympathetic regulation, multiple other neuronal signaling cascades have been implicated in the complex neuronal-bone interaction, namely, melanocortin-4 receptor, Y-receptor, cannabinoid receptor, and neuromedin U (**Bajayo et al., 2005**; **Baldock et al., 2002**; **Karsak et al., 2005**; **Ofek et al., 2006**; **Sato et al., 2007**; **Shi and Baldock, 2012**). The peripheral cannabinoid receptor (CB2) that regulates appetite and energy balance also regulates bone turnover by modulating sympathetic innervation. Mice with a targeted deletion of *Cb2* gene show markedly accelerated age-related trabecular bone loss and cortical expansion with high bone turnover (**Ofek et al., 2006**) In addition, GWAS showed an association of a single polymorphism and haplotype encompassing *CB2* gene on human chromosome 1p36 (**Karsak et al., 2005**). On the other hand, the central cannabinoid receptor type 1 (CB1), which is present in sympathetic terminals, interacts with endocannabinoid 2-arachidonoylglycerol to suppress norepinephrine release and prevent Adrb2 activation in bone, resulting in increased bone mass (**Tam et al., 2008**). Further, upregulating the NO-cGMP-PKG signaling by inhibiting phosphodiesterase (PDE)-5A, which expressed in sympathetic neurons of the locus coeruleus, raphe pallidus, and paraventricular nucleus of the hypothalamus, suppresses bone remodeling (**Kim et al., 2020b**). In addition, recent studies show that sympathetic nerves that richly innervate the vestibular cells of the inner ear also regulate bone remodeling peripherally. In fact, bilateral vestibular lesions in mice caused peripheral bone loss due to decreased bone formation and increased resorption (**Vignaux et al., 2015**). This finding may be relevant to the osteoblast dysfunction in elderly patients with osteoporosis, many of whom also have vestibular dysfunction.

Given the extensive central regulation of skeletal homeostasis, it comes as no surprise that the bone can also signal back to the brain to modulate this regulation. Recent findings indicate that bone-derived signals can affect cognitive function and fetal brain development. GPCRs for osteocalcin, namely Gpr158, have been identified in brain (**Khrimian et al., 2017**; **Obri et al., 2018**), and uncarboxylated osteocalcin (GluOCN) has been shown to cross the blood-brain barrier to accumulate in specific regions of the brain, primarily the midbrain and brainstem (**Oury et al., 2013**). Furthermore, osteocalcin-deficient mice demonstrated a behavioral phenotype of passivity (**Ducy et al., 1996**; **Obri et al., 2018**) independently of abnormal glucose homeostasis (**Pi et al., 2008**). In addition to behavioral changes, osteocalcin-deficient mice of both sexes also displayed major deficits in learning and memory (**Oury et al., 2013**). Further anatomic examination revealed smaller brain sizes—the dentate gyrus of the hippocampus was 30% smaller and the corpus callosum was often missing, both of which are consistent with decreased spatial learning and memory (**Oury et al., 2013**). At a biochemical level, the midbrain and brainstem of osteocalcin-deficient mice had significantly lower amounts of monoamine neurotransmitters, including dopamine, serotonin, and norepinephrine. There was also significantly higher accumulation of the inhibitory neurotransmitter GABA in the same regions (**Oury et al., 2013**). These finding are supported by intracerebroventricular infusions of osteocalcin in $Ocn^{-/-}$ mice that rescued the anxiety and depression phenotypes (**Oury et al., 2013**). Furthermore, injections of plasma from wild type mice and osmotic pumps delivering osteocalcin rescued defects in cognition and anxiety (**Khrimian et al., 2017**). Taken together, these findings show that osteocalcin regulates neurotransmitter synthesis and affect behavior.

Bone is molecularly tied to muscle

Situated close to each other, bone and muscle work as a functional unit, clinically demonstrated by the fact that osteoporosis occurs with sarcopenia (**Edwards et al., 2015**). Spinal cord injury, which is associated with severe osteoporosis and progressive muscle loss, is a striking example of the functional interdependence of muscle and bone (**Bauman et al., 1999**). Spinal cord injury-induced bone resorption and bone loss are normalized after electrical stimulation of denervated muscle in rats (**Qin et al., 2013**), which suggests a non-neural, molecular connection between bone and muscle.

Skeletal muscle is indeed a recognized endocrine organ, secreting numerous cytokines and growth factors, collectively termed myokines (**Gomarasca et al., 2020**). Irisin, released upon exercise, is a suspected candidate for a non-neural, bone-muscle link. Irisin administered to rodents increased

bone mass by enhancing ERK signaling and upregulating expression of the osteoblastogenic genes *Atf4*, *Runx2*, *Osx*, *Lrp5,* and *β-catenin* (**Colaianni et al., 2014**; **Colaianni et al., 2015**; **Zhang et al., 2017**). Surprisingly, irisin did not only increase bone formation by inhibiting sclerostin expression, but also suppressed RANKL-induced osteoclastogenesis (**Zhang et al., 2017**). In contrast, myostatin, a member of the TGFβ superfamily, regulates osteogenesis negatively. Myostatin deficiency results in an overall increase in bone density, strength, and mineralization (**Carnac et al., 2007**; **Eijken et al., 2007**; **Elkasrawy and Hamrick, 2010**; **McPherron et al., 1997**). Myostatin is overexpressed in bone of diabetic $Lepr^{db-/-}$ mice with a tibial defect. Inhibiting myostatin by direct injection of its antagonist, follistatin into the site of the defect, resulted in improved bone regeneration, osteoblast proliferation and differentiation, and calcification. Taken together, these findings indicate that follistatin exerts a pro-osteogenic effect secondary to myostatin blockade (**Amthor et al., 2004**; **Cash et al., 2009**; **Wallner et al., 2017**). The negative skeletal remodeling induced by myostatin appears to be the result of suppressed WNT signaling. In murine osteocytes, myostatin-induced epigenetic changes through osteocyte-derived microRNA-218 (miR-218) and other exosomes has been shown to increase sclerostin and DKK1 expression, resulting ultimately in suppressed osteoblastogenesis (**Li et al., 2016**; **Qin et al., 2017**).

The deletion of bone-specific, muscle-specific, or commonly expressed genes in both bone and muscle cells also provide further insights into the muscle-bone connection. The osteocyte-specific deletion of the MBTPS1 protease increased muscle regeneration by upregulation of *Pax7*, *Myog*, *Myod1*, *Notch,* and *Myh3* expression resulting in increased muscle mass and contractility (**Gorski et al., 2016**). Further, skeletal muscle-specific deletion of the *Baml1* gene, which encodes a molecular clock transcription factor, impaired muscle function, but caused bone and cartilage defects (**Schroder et al., 2015**). Likewise, osteocalcin, which is primarily secreted from bone cells, promotes nutrient uptake in myofibers with exercise (**Mera et al., 2016a**; **Mera et al., 2016b**). The downregulation of methyltransferase 21C, which methylate chaperones in bone and muscle, reduces myogenesis as well as osteocyte survival (**Huang et al., 2014**). Similarly, ryanodine receptors integrate cytosolic Ca^{2+} signals in both osteoclasts and muscle cells (**Zaidi et al., 1989**; **Zaidi et al., 1992**; **Zaidi et al., 1995**).

Bone connects to fat and energy homeostasis

Bone and adipose tissue remodeling occur through a complex neuroendocrine circuit that involves the brain, pituitary gland, adipose depots, and the skeleton. As noted above, a non-classical action of FSH was implicated not only in bone remodeling (see above), but also in promoting adipogenicity. The perimenopausal transition, which is accompanied by the early rise of FSH followed by estrogen deficiency, is associated with increased visceral obesity and dysregulated energy homeostasis. Our group has shown that inhibiting FSH signaling both genetically in $Fshr^{+/-}$ mice and pharmacologically using an FSH-blocking antibodies in mice dramatically reduces fat in all depots, including bone marrow, and induces thermogenic beige adipose tissue (**Gera et al., 2020**; **Zhu et al., 2012a**). This action is exerted through high-affinity FSHRs present on both white and brown adipocytes (**Liu et al., 2017**).

The interaction of the skeleton with the brain and fat is, in part, mediated by adipokines and the SNS. Leptin- and leptin receptor-deficient mice are phenotypically obese and hypogonadal (**Ducy et al., 2000**). Adiponectin partially counteracts leptin's action by decreasing sympathetic tone, which is opposed by its peripheral effect by suppressing osteoblastogenesis directly (**Kajimura et al., 2013**). Also worth noting is that fatty acids secreted by adipocytes, such as palmitate, exert a lipotoxic effect on osteoblasts and osteocytes and their precursors in the bone marrow (**Al Saedi et al., 2019**; **Gunaratnam et al., 2014**). 'Hunger hormones' such as peptide Y and ghrelin have also been linked to bone loss in patients after gastric bypass due to a paradoxical increase in bone marrow fat (**Kim et al., 2020a**).

The role of osteocalcin in glucose homeostasis is also noteworthy. GluOCN binds to the GPR6A to stimulate pancreatic β-cell proliferation and insulin secretion; in turn, insulin favors GluOCN bioactivity (**Ferron et al., 2008**; **Fulzele et al., 2010**; **Pi et al., 2011**; **Wei et al., 2014b**). Osteoblast-specific insulin receptor-deficient mice showed low levels of GluOCN with reduced bone formation. These mice developed obesity and insulin resistance with aging, which was improved by GluOCN administration (**Fulzele et al., 2010**). Additionally, delta like-1 (DLK) protein, which is expressed by the pancreas in response to GluOCN and counteracts the stimulatory effect of insulin on osteoblast proliferation (**Abdallah et al., 2015**). Likewise, leptin-induced SNS activation results in the upregulation of

osteotesticular phosphatase, which inhibits osteocalcin activity (**Hinoi et al., 2008**). Finally, osteocalcin not only works as an insulin secretagogue, but also improves insulin sensitivity. Daily administration of GluOCN in mice increased mitochondrial activity in skeletal tissue, associated with increased energy expenditure (**Ferron et al., 2012**). Obese mice with insulin resistance after high-fat diet displayed decreased GluOCN levels (**Wei et al., 2014a**). Observational data in humans is, however, somewhat conflicting due to confounding factors and heterogenous study designs. In type 1 diabetes patients, GluOCN was positively associated with the C-peptide/glucose ratio (**Thrailkill et al., 2012**); however, osteoporotic patients receiving bisphosphonates, known to suppress bone turnover, did not show a correlation between GluOCN levels and glucose homeostasis parameters, such as fasting glucose or insulin levels (**Hong et al., 2013**).

Lastly, interest in bone marrow fat has gained significant traction in recent years as aging in both sexes and menopause in women are associated with profound increases in bone marrow fat deposition (**Suchacki et al., 2016**). Bone marrow adipocytes, interestingly, display a signature of osteogenic precursor markers, such as *Osx*, *Runx2,* and *Lepr*, suggesting a mesenchymal origin, as with osteoblasts (**Matic et al., 2016b**). Some consider BMSC differentiation into a bone marrow adipocyte as the default, unless it is committed to the osteoblast lineage (**Pierce et al., 2019**). The expression of PPARγ, CCAAT/enhancer-binding protein α, and secreted frizzled related protein 1 promote BMSC commitment to bone marrow adipocyte differentiation, whereas IGF-1 and adiponectin inhibit adipocyte differentiation (**Tencerova and Kassem, 2016**). Thus, patients receiving thiazolidinedione develop osteopenia as PPARγ activation stimulates adipogenesis at the expense of osteoblastogenesis (**Cawthorn et al., 2014**; **Lu et al., 2016**; **Tsuchida et al., 2005**). And LepR signaling in BMSC promotes adipogenesis and inhibits osteoblastogenesis in response to diet (**Yue et al., 2016**). The zinc finger nuclease, ZFP467, also plays a role in determining BMSC fate (**Quach et al., 2011**). ZFP467-deficient mice demonstrate increased trabecular bone volume and a significant reduction in marrow adipose tissue (**Le et al., 2021**). The osteoanabolic and anti-adipogenic effects of PTH are, in part, mediated by suppressing *Zfp467* expression (**Fan et al., 2017**; **Le et al., 2021**). A recent study has shown that a subpopulation of BMSCs, called marrow adipogenic lineage precursors, express RANKL and regulate osteoclastic bone resorption (**Yu et al., 2021**).

Bone talks to other vital organs

Vital organs function in coordination to maintain bodily homeostasis, and this crosstalk between organs is achieved through complex biological communications and feedback mediated through cellular, soluble, and neurohormonal pathways (**Armutcu, 2019**). For example, fibroblast growth factor (FGF) 23 from osteocytes binds to the FGF receptor 1-Klotho complex in the kidney to promote phosphate excretion (**Nakatani et al., 2009**; **Shimada et al., 2004**; **Shimada et al., 2001**). Clinical observation of decreased bone mass in patients with pathologies of other vital organs has provided additional insight into the integrative nature of skeletal physiology. For example, osteoporosis and osteopenia are prevalent with chronic liver diseases, especially with cholestatic liver disease (**Ninkovic et al., 2002**). In vitro studies have shown that treatment with unconjugated bilirubin or serum from jaundiced patients significantly reduced viability and differentiation of osteoblast-like cells and primary osteoblasts (**Janes et al., 1995**; **Ruiz-Gaspà et al., 2011**), with a significantly increased RANKL/OPG ratio (**Ruiz-Gaspà et al., 2011**). Taurine, which is primarily synthesized in liver, mediates GH-dependent IGF-1 synthesis and subsequently enhances osteoblast function (**Clemens, 2014**). Since vitamin B_{12} is required for taurine synthesis, the deletion of gastric intrinsic factor causes low bone mass in mice, which is subsequently rescued by taurine supplementation (**Clemens, 2014**; **Roman-Garcia et al., 2014**). Likewise, patients with chronic obstructive pulmonary disease, even when clinically stable, often demonstrate increased inflammatory markers and lower BMD (**Liang and Feng, 2012**). The association of heart disease and osteoporosis is also worth noting. Secondary hyperparathyroidism can occur in patients with heart failure independent of renal function (**Altay et al., 2012**). Moreover, upregulation of the renin-angiotensin-aldosterone (RAA) axis in heart failure might promote RANKL expression and osteoclast differentiation (**Guan et al., 2011**). In all, the skeleton is directly and indirectly intertwined with other vital organs, and new advances in integrative physiology continue to expand the breadth of our understanding of skeletal physiology.

The impact of aging and sex

Aging-related dysfunction in non-skeletal organ can affect skeletal homeostasis. Decreased organ function and chronic inflammation with aging, which cause changes in hemodynamics, RAA system, and SNS, can disturb bone remodeling (***Oishi and Manabe, 2020***). The Wnt-related proteins were shown to be downregulated in osteoblasts with aging (***Rauner et al., 2008***), which was partly mediated by increased endogenous glucocorticoids and oxidized lipid-induced PPARγ activation (***Manolagas, 2010***). In addition, aging-associated changes in HSCs may cause aggressive osteoclastic bone resorption (***Møller et al., 2020***).

Sex undoubtedly has a major impact on organ crosstalk. Many factors, including sex-specific genes, genetic imprinting, and sex steroids, are involved in the regulation of key signaling pathways. For example, the difference in the relative levels of calcification and fibrosis in heart valves in male and female may be attributed to differences in BMP/TGFβ signaling (***Shah and Rogers, 2018***). Notably, estrogen directly induces *Bmp2* and *Bmp6* transcription (***Zhou et al., 2003***) and stimulates SMAD-2/3 protein degradation (***Ito et al., 2010***).

Possible new medicines

Understanding the integrative nature of skeletal physiology has opened up the potential for new therapeutic targets for osteoporosis. Osteo-induction by BMPs has long been utilized to accelerate fracture healing, with recombinant human BMP-2 use approved in bone grafts for treating acute, open tibial shaft fractures (***Salazar et al., 2016***). Our group recently developed a fully humanized, multipurpose blocking antibody specific to FSHβ targeting both postmenopausal osteoporosis and the accompanying visceral obesity and neurodegeneration (***Gera et al., 2020***). Upregulating LXR activity has been explored as it suppresses osteoclastogenesis and confers cardioprotection, making LXR agonists a potential dual treatment for osteoporosis and cardiovascular disease (***Kleyer et al., 2012***; ***Ma et al., 2017***). Osteocalcin, given that it regulates bone remodeling, glucose, and energy homeostasis, and seems to be involved in age-related cognitive decline, is a promising multisystem therapeutic target (***Obri et al., 2018***).

Due to the common signaling pathways involved in the homeostasis of bone and other organ systems, using existing pharmacotherapies in different applications is also possible. For example, our group showed that nitrogen-containing bisphosphonates can directly inhibit the growth of EGFR-driven cancer cells, making it possible to potentially repurpose them to treat lung, breast, gastrointestinal, head and neck, and other cancers (***Stachnik et al., 2014***; ***Yuen et al., 2014***). PDE5 inhibitors, a class of commonly used drugs for treating erectile dysfunction and pulmonary hypertension, have shown a combined anabolic and anti-resorptive action in the skeleton (***Kim et al., 2020b***), highlighting the possibility of targeting the NO-cGMP-PKG pathway in treating osteoporosis (***Kim et al., 2020c***). Similarly, meclizine, an anti-histamine used for treating vertigo and motion sickness, is being tested for its ability to enhance growth in achondroplasia by inhibiting FGF receptor 3, a negative regulator of endochondral bone growth (***Matsushita et al., 2015***). Lastly, statins, which block HMG-CoA reductase, promote bone formation in rats (; ***Zhu et al., 2021***). Conversely, the lack of HMG-CoA reductase decreases osteoclast survival, indicating the possibility of repurposing statins for treating bone loss (***Luegmayr et al., 2004***).

In sum, recent interest in skeletal physiology in the context of intercellular and interorgan communication affords a myriad of translational and clinical possibilities. The complex crosstalk links seemingly divergent processes and systems increasingly intimately, with new therapeutic targets being identified at a rapid rate. As implied above, these discoveries are paving the way for a new clinical paradigm, one that entails using single agent to treat multiple, co-existing diseases.

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References

Abdallah BM, Ditzel N, Laborda J, Karsenty G, Kassem M. 2015. DLK1 regulates whole-body glucose metabolism: A negative feedback regulation of the osteocalcin-insulin loop. *Diabetes* **64**:3069–3080. DOI: https://doi.org/10.2337/db14-1642, PMID: 25918236

Abe E, Marians RC, Yu W, Wu X-B, Ando T, Li Y, Iqbal J, Eldeiry L, Rajendren G, Blair HC, Davies TF, Zaidi M. 2003. Tsh is a negative regulator of skeletal remodeling. *Cell* **115**:151–162. DOI: https://doi.org/10.1016/S0092-8674(03)00771-2, PMID: 14567913

Adami S, Bianchi G, Brandi ML, Giannini S, Ortolani S, DiMunno O, Frediani B, Rossini M, BONTURNO study group. 2008. Determinants of bone turnover markers in healthy premenopausal women. *Calcified Tissue International* **82**:341–347. DOI: https://doi.org/10.1007/s00223-008-9126-5, PMID: 18470550

Al Saedi A, Bermeo S, Plotkin L, Myers DE, Duque G. 2019. Mechanisms of palmitate-induced lipotoxicity in osteocytes. *Bone* **127**:353–359. DOI: https://doi.org/10.1016/j.bone.2019.06.016, PMID: 31226530

Altay H, Zorlu A, Binici S, Bilgi M, Yilmaz MB, Colkesen Y, Erol T, Muderrisoglu H. 2012. Relation of serum parathyroid hormone level to severity of heart failure. *The American Journal of Cardiology* **109**:252–256. DOI: https://doi.org/10.1016/j.amjcard.2011.08.039, PMID: 21996143

Amthor H, Nicholas G, McKinnell I, Kemp CF, Sharma M, Kambadur R, Patel K. 2004. Follistatin complexes myostatin and antagonises myostatin-mediated inhibition of myogenesis. *Developmental Biology* **270**:19–30. DOI: https://doi.org/10.1016/j.ydbio.2004.01.046, PMID: 15136138

Arai F, Hirao A, Ohmura M, Sato H, Matsuoka S, Takubo K, Ito K, Koh GY, Suda T. 2004. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. *Cell* **118**:149–161. DOI: https://doi.org/10.1016/j.cell.2004.07.004, PMID: 15260986

Armutcu F. 2019. Organ crosstalk: the potent roles of inflammation and fibrotic changes in the course of organ interactions. *Inflammation Research* **68**:825–839. DOI: https://doi.org/10.1007/s00011-019-01271-7, PMID: 31327029

Arnett TR, Dempster DW. 1986. Effect of ph on bone resorption by rat osteoclasts in vitro. *Endocrinology* **119**:119–124. DOI: https://doi.org/10.1210/endo-119-1-119, PMID: 3720660

Asagiri M, Sato K, Usami T, Ochi S, Nishina H, Yoshida H, Morita I, Wagner EF, Mak TW, Serfling E, Takayanagi H. 2005. Autoamplification of nfatc1 expression determines its essential role in bone homeostasis. *The Journal of Experimental Medicine* **202**:1261–1269. DOI: https://doi.org/10.1084/jem.20051150, PMID: 16275763

Aubert CE, Floriani C, Bauer DC, da Costa BR, Segna D, Blum MR, Collet T-H, Fink HA, Cappola AR, Syrogiannouli L, Peeters RP, Åsvold BO, den Elzen WPJ, Luben RN, Bremner AP, Gogakos A, Eastell R, Kearney PM, Hoff M, Le Blanc E, et al. 2017. Thyroid function tests in the reference range and fracture: individual participant analysis of prospective cohorts. *The Journal of Clinical Endocrinology and Metabolism* **102**:2719–2728. DOI: https://doi.org/10.1210/jc.2017-00294, PMID: 28482002

Bajayo A, Goshen I, Feldman S, Csernus V, Iverfeldt K, Shohami E, Yirmiya R, Bab I. 2005. Central IL-1 receptor signaling regulates bone growth and mass. *PNAS* **102**:12956–12961. DOI: https://doi.org/10.1073/pnas.0502562102, PMID: 16126903

Bajayo A, Bar A, Denes A, Bachar M, Kram V, Attar-Namdar M, Zallone A, Kovács KJ, Yirmiya R, Bab I. 2012. Skeletal parasympathetic innervation communicates central IL-1 signals regulating bone mass accrual. *PNAS* **109**:15455–15460. DOI: https://doi.org/10.1073/pnas.1206061109, PMID: 22949675

Baldock PA, Sainsbury A, Couzens M, Enriquez RF, Thomas GP, Gardiner EM, Herzog H. 2002. Hypothalamic Y2 receptors regulate bone formation. *The Journal of Clinical Investigation* **109**:915–921. DOI: https://doi.org/10.1172/JCI14588, PMID: 11927618

Baliram R, Latif R, Berkowitz J, Frid S, Colaianni G, Sun L, Zaidi M, Davies TF. 2011. Thyroid-stimulating hormone induces a wnt-dependent, feed-forward loop for osteoblastogenesis in embryonic stem cell cultures. *PNAS* **108**:16277–16282. DOI: https://doi.org/10.1073/pnas.1110286108, PMID: 21911383

Baliram R, Sun L, Cao J, Li J, Latif R, Huber AK, Yuen T, Blair HC, Zaidi M, Davies TF. 2012. Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH signaling. *The Journal of Clinical Investigation* **122**:3737–3741. DOI: https://doi.org/10.1172/JCI63948, PMID: 22996689

Baliram R, Chow A, Huber AK, Collier L, Ali MR, Morshed SA, Latif R, Teixeira A, Merad M, Liu L, Sun L, Blair HC, Zaidi M, Davies TF. 2013. Thyroid and bone: macrophage-derived TSH-β splice variant increases murine osteoblastogenesis. *Endocrinology* **154**:4919–4926. DOI: https://doi.org/10.1210/en.2012-2234, PMID: 24140716

Baliram R., Latif R, Morshed SA, Zaidi M, Davies TF. 2016. T3 regulates a human macrophage-derived TSH-β splice variant: implications for human bone biology. *Endocrinology* **157**:3658–3667. DOI: https://doi.org/10.1210/en.2015-1974, PMID: 27300765

Barrow AD, Raynal N, Andersen TL, Slatter DA, Bihan D, Pugh N, Cella M, Kim T, Rho J, Negishi-Koga T, Delaisse J-M, Takayanagi H, Lorenzo J, Colonna M, Farndale RW, Choi Y, Trowsdale J. 2011. Oscar is a collagen receptor that costimulates osteoclastogenesis in DAP12-deficient humans and mice. *The Journal of Clinical Investigation* **121**:3505–3516. DOI: https://doi.org/10.1172/JCI45913, PMID: 21841309

Bassett JHD, Williams AJ, Murphy E, Boyde A, Howell PGT, Swinhoe R, Archanco M, Flamant F, Samarut J, Costagliola S, Vassart G, Weiss RE, Refetoff S, Williams GR. 2008. A lack of thyroid hormones rather than excess thyrotropin causes abnormal skeletal development in hypothyroidism. *Molecular Endocrinology* **22**:501–512. DOI: https://doi.org/10.1210/me.2007-0221, PMID: 17932107

Bauman WA, Spungen AM, Wang J, Pierson RN, Schwartz E. 1999. Continuous loss of bone during chronic immobilization: a monozygotic twin study. *Osteoporosis International* **10**:123–127. DOI: https://doi.org/10.1007/s001980050206, PMID: 10501792

Bouillon R. 1991. Growth hormone and bone. *Hormone Research* **36 Suppl 1**:49–55. DOI: https://doi.org/10.1159/000182189, PMID: 1806485

Boutin A, Gershengorn MC, Neumann S. 2020. β-arrestin 1 in thyrotropin receptor signaling in bone: studies in osteoblast-like cells. *Frontiers in Endocrinology* **11**:312. DOI: https://doi.org/10.3389/fendo.2020.00312, PMID: 32508750

Boyden LM, Mao J, Belsky J, Mitzner L, Farhi A, Mitnick MA, Wu D, Insogna K, Lifton RP. 2002. High bone density due to a mutation in LDL-receptor-related protein 5. *The New England Journal of Medicine* **346**:1513–1521. DOI: https://doi.org/10.1056/NEJMoa013444, PMID: 12015390

Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, Martin RP, Schipani E, Divieti P, Bringhurst FR, Milner LA, Kronenberg HM, Scadden DT. 2003. Osteoblastic cells regulate the haematopoietic stem cell niche. *Nature* **425**:841–846. DOI: https://doi.org/10.1038/nature02040, PMID: 14574413

Canalis E, Schilling L, Yee SP, Lee SK, Zanotti S. 2016. Hajdu cheney mouse mutants exhibit osteopenia, increased osteoclastogenesis, and bone resorption. *The Journal of Biological Chemistry* **291**:1538–1551. DOI: https://doi.org/10.1074/jbc.M115.685453, PMID: 26627824

Cannon JG, Cortez-Cooper M, Meaders E, Stallings J, Haddow S, Kraj B, Sloan G, Mulloy A. 2010. Follicle-stimulating hormone, interleukin-1, and bone density in adult women. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **298**:R790–R798. DOI: https://doi.org/10.1152/ajpregu.00728.2009, PMID: 20042686

Cannon JG, Kraj B, Sloan G. 2011. Follicle-stimulating hormone promotes RANK expression on human monocytes. *Cytokine* **53**:141–144. DOI: https://doi.org/10.1016/j.cyto.2010.11.011, PMID: 21159522

Carnac G, Vernus B, Bonnieu A. 2007. Myostatin in the pathophysiology of skeletal muscle. *Current Genomics* **8**:415–422. DOI: https://doi.org/10.2174/138920207783591672, PMID: 19412331

Cash JN, Rejon CA, McPherron AC, Bernard DJ, Thompson TB. 2009. The structure of myostatin: follistatin 288: insights into receptor utilization and heparin binding. *The EMBO Journal* **28**:2662–2676. DOI: https://doi.org/10.1038/emboj.2009.205, PMID: 19644449

Cassier E, Gallay N, Bourquard T, Claeysen S, Bockaert J, Crépieux P, Poupon A, Reiter E, Marin P, Vandermoere F. 2017. Phosphorylation of β-arrestin2 at thr^{383} by MEK underlies β-arrestin-dependent activation of erk1/2 by gpcrs. *eLife* **6**:e23777. DOI: https://doi.org/10.7554/eLife.23777, PMID: 28169830

Castro-Mollo M, Gera S, Ruiz-Martinez M, Feola M, Gumerova A, Planoutene M, Clementelli C, Sangkhae V, Casu C, Kim S-M, Ostland V, Han H, Nemeth E, Fleming R, Rivella S, Lizneva D, Yuen T, Zaidi M, Ginzburg Y. 2021. The hepcidin regulator erythroferrone is a new member of the erythropoiesis-iron-bone circuitry. *eLife* **10**:e68217. DOI: https://doi.org/10.7554/eLife.68217, PMID: 34002695

Cawthorn WP, Scheller EL, Learman BS, Parlee SD, Simon BR, Mori H, Ning X, Bree AJ, Schell B, Broome DT, Soliman SS, DelProposto JL, Lumeng CN, Mitra A, Pandit SV, Gallagher KA, Miller JD, Krishnan V, Hui SK, Bredella MA, et al. 2014. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. *Cell Metabolism* **20**:368–375. DOI: https://doi.org/10.1016/j.cmet.2014.06.003, PMID: 24998914

Cheung E, Tsang S, Bow C, Soong C, Yeung S, Loong C, Cheung C-L, Kan A, Lo S, Tam S, Tang G, Kung A. 2011. Bone loss during menopausal transition among southern chinese women. *Maturitas* **69**:50–56. DOI: https://doi.org/10.1016/j.maturitas.2011.01.010, PMID: 21310558

Clemens TL. 2014. Vitamin B12 deficiency and bone health. *The New England Journal of Medicine* **371**:963–964. DOI: https://doi.org/10.1056/NEJMcibr1407247, PMID: 25184870

Colaianni G, Cuscito C, Mongelli T, Oranger A, Mori G, Brunetti G, Colucci S, Cinti S, Grano M. 2014. Irisin enhances osteoblast differentiation in vitro. *International Journal of Endocrinology* **2014**:902186. DOI: https://doi.org/10.1155/2014/902186, PMID: 24723951

Colaianni G, Cuscito C, Mongelli T, Pignataro P, Buccoliero C, Liu P, Lu P, Sartini L, Di Comite M, Mori G, Di Benedetto A, Brunetti G, Yuen T, Sun L, Reseland JE, Colucci S, New MI, Zaidi M, Cinti S, Grano M. 2015. The myokine irisin increases cortical bone mass. *PNAS* **112**:12157–12162. DOI: https://doi.org/10.1073/pnas.1516622112, PMID: 26374841

Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbini CAF, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C, Grauer A. 2016. Romosozumab treatment in postmenopausal women with osteoporosis. *The New England Journal of Medicine* **375**:1532–1543. DOI: https://doi.org/10.1056/NEJMoa1607948, PMID: 27641143

Coss D, Yang L, Kuo CB, Xu X, Luben RA, Walker AM. 2000. Effects of prolactin on osteoblast alkaline phosphatase and bone formation in the developing rat. *American Journal of Physiology. Endocrinology and Metabolism* **279**:E1216–E1225. DOI: https://doi.org/10.1152/ajpendo.2000.279.6.E1216, PMID: 11093907

Devlin RD, Du Z, Pereira RC, Kimble RB, Economides AN, Jorgetti V, Canalis E. 2003. Skeletal overexpression of noggin results in osteopenia and reduced bone formation. *Endocrinology* **144**:1972–1978. DOI: https://doi.org/10.1210/en.2002-220918, PMID: 12697704

Ducy P, Desbois C, Boyce B, Pinero G, Story B, Dunstan C, Smith E, Bonadio J, Goldstein S, Gundberg C, Bradley A, Karsenty G. 1996. Increased bone formation in osteocalcin-deficient mice. *Nature* **382**:448–452. DOI: https://doi.org/10.1038/382448a0, PMID: 8684484

Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, Shen J, Vinson C, Rueger JM, Karsenty G. 2000. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell* **100**:197–207. DOI: https://doi.org/10.1016/s0092-8674(00)81558-5, PMID: 10660043

Edwards MH, Dennison EM, Aihie Sayer A, Fielding R, Cooper C. 2015. Osteoporosis and sarcopenia in older age. *Bone* **80**:126–130. DOI: https://doi.org/10.1016/j.bone.2015.04.016, PMID: 25886902

Eijken M, Swagemakers S, Koedam M, Steenbergen C, Derkx P, Uitterlinden AG, van der Spek PJ, Visser JA, de Jong FH, Pols HAP, van Leeuwen JPTM. 2007. The activin A-follistatin system: potent regulator of human extracellular matrix mineralization. *FASEB Journal* **21**:2949–2960. DOI: https://doi.org/10.1096/fj.07-8080com, PMID: 17449718

Elefteriou F, Ahn JD, Takeda S, Starbuck M, Yang X, Liu X, Kondo H, Richards WG, Bannon TW, Noda M, Clement K, Vaisse C, Karsenty G. 2005. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature* **434**:514–520. DOI: https://doi.org/10.1038/nature03398, PMID: 15724149

Elkasrawy MN, Hamrick MW. 2010. Myostatin (GDF-8) as a key factor linking muscle mass and bone structure. *Journal of Musculoskeletal & Neuronal Interactions* **10**:56–63 PMID: 20190380.

Engin F, Yao Z, Yang T, Zhou G, Bertin T, Jiang MM, Chen Y, Wang L, Zheng H, Sutton RE, Boyce BF, Lee B. 2008. Dimorphic effects of Notch signaling in bone homeostasis. *Nature Medicine* **14**:299–305. DOI: https://doi.org/10.1038/nm1712, PMID: 18297084

Epstein S, Inzerillo AM, Caminis J, Zaidi M. 2003. Disorders associated with acute rapid and severe bone loss. *Journal of Bone and Mineral Research* **18**:2083–2094. DOI: https://doi.org/10.1359/jbmr.2003.18.12.2083, PMID: 14672343

Evans CH. 2007. John Hunter and the origins of modern orthopaedic research. *Journal of Orthopaedic Research* **25**:556–560. DOI: https://doi.org/10.1002/jor.20386, PMID: 17340637

Fan Y, Hanai J-I, Le PT, Bi R, Maridas D, DeMambro V, Figueroa CA, Kir S, Zhou X, Mannstadt M, Baron R, Bronson RT, Horowitz MC, Wu JY, Bilezikian JP, Dempster DW, Rosen CJ, Lanske B. 2017. Parathyroid hormone directs bone marrow mesenchymal cell fate. *Cell Metabolism* **25**:661–672. DOI: https://doi.org/10.1016/j.cmet.2017.01.001, PMID: 28162969

Ferron M, Hinoi E, Karsenty G, Ducy P. 2008. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. *PNAS* **105**:5266–5270. DOI: https://doi.org/10.1073/pnas.0711119105, PMID: 18362359

Ferron M, McKee MD, Levine RL, Ducy P, Karsenty G. 2012. Intermittent injections of osteocalcin improve glucose metabolism and prevent type 2 diabetes in mice. *Bone* **50**:568–575. DOI: https://doi.org/10.1016/j.bone.2011.04.017, PMID: 21550430

Fleming HE, Janzen V, Lo Celso C, Guo J, Leahy KM, Kronenberg HM, Scadden DT. 2008. Wnt signaling in the niche enforces hematopoietic stem cell quiescence and is necessary to preserve self-renewal in vivo. *Cell Stem Cell* **2**:274–283. DOI: https://doi.org/10.1016/j.stem.2008.01.003, PMID: 18371452

Fritton JC, Emerton KB, Sun H, Kawashima Y, Mejia W, Wu Y, Rosen CJ, Panus D, Bouxsein M, Majeska RJ, Schaffler MB, Yakar S. 2010. Growth hormone protects against ovariectomy-induced bone loss in states of low circulating insulin-like growth factor (IGF-1). *Journal of Bone and Mineral Research* **25**:235–246. DOI: https://doi.org/10.1359/jbmr.090723, PMID: 19619004

Fu L, Patel MS, Bradley A, Wagner EF, Karsenty G. 2005. The molecular clock mediates leptin-regulated bone formation. *Cell* **122**:803–815. DOI: https://doi.org/10.1016/j.cell.2005.06.028, PMID: 16143109

Fuentealba LC, Eivers E, Ikeda A, Hurtado C, Kuroda H, Pera EM, De Robertis EM. 2007. Integrating patterning signals: wnt/GSK3 regulates the duration of the BMP/smad1 signal. *Cell* **131**:980–993. DOI: https://doi.org/10.1016/j.cell.2007.09.027, PMID: 18045539

Fulciniti M, Tassone P, Hideshima T, Vallet S, Nanjappa P, Ettenberg SA, Shen Z, Patel N, Tai Y-T, Chauhan D, Mitsiades C, Prabhala R, Raje N, Anderson KC, Stover DR, Munshi NC. 2009. Anti-DKK1 mab (BHQ880) as a potential therapeutic agent for multiple myeloma. *Blood* **114**:371–379. DOI: https://doi.org/10.1182/blood-2008-11-191577, PMID: 19417213

Fulzele K, Riddle RC, DiGirolamo DJ, Cao X, Wan C, Chen D, Faugere M-C, Aja S, Hussain MA, Brüning JC, Clemens TL. 2010. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. *Cell* **142**:309–319. DOI: https://doi.org/10.1016/j.cell.2010.06.002, PMID: 20655471

Gallagher CM, Moonga BS, Kovach JS. 2010. Cadmium, follicle-stimulating hormone, and effects on bone in women age 42–60 years, NHANES III. *Environmental Research* **110**:105–111. DOI: https://doi.org/10.1016/j.envres.2009.09.012, PMID: 19875111

Gera S, Sant D, Haider S, Korkmaz F, Kuo TC, Mathew M, Perez-Pena H, Xie H, Chen H, Batista R, Ma K, Cheng Z, Hadelia E, Robinson C, Macdonald A, Miyashita S, Williams A, Jebian G, Miyashita H, Gumerova A, et al. 2020. First-in-class humanized FSH blocking antibody targets bone and fat. *PNAS* **117**:28971–28979. DOI: https://doi.org/10.1073/pnas.2014588117, PMID: 33127753

Gomarasca M, Banfi G, Lombardi G. 2020. Myokines: the endocrine coupling of skeletal muscle and bone. *Advances in Clinical Chemistry* **94**:155–218. DOI: https://doi.org/10.1016/bs.acc.2019.07.010, PMID: 31952571

Gorski JP, Huffman NT, Vallejo J, Brotto L, Chittur SV, Breggia A, Stern A, Huang J, Mo C, Seidah NG, Bonewald L, Brotto M. 2016. Deletion of mbtps1 (pcsk8, s1p, ski-1) gene in osteocytes stimulates soleus muscle regeneration and increased size and contractile force with age. *The Journal of Biological Chemistry* **291**:4308–4322. DOI: https://doi.org/10.1074/jbc.M115.686626, PMID: 26719336

Govoni KE, Wergedal JE, Florin L, Angel P, Baylink DJ, Mohan S. 2007. Conditional deletion of insulin-like growth factor-I in collagen type 1alpha2-expressing cells results in postnatal lethality and a dramatic reduction in bone accretion. *Endocrinology* **148**:5706–5715. DOI: https://doi.org/10.1210/en.2007-0608, PMID: 17717052

Guan XX, Zhou Y, Li JY. 2011. Reciprocal roles of angiotensin II and angiotensin II receptors blockade (ARB) in regulating cbfa1/RANKL via camp signaling pathway: possible mechanism for hypertension-related osteoporosis and antagonistic effect of ARB on hypertension-related osteoporosis. *International Journal of Molecular Sciences* **12**:4206–4213. DOI: https://doi.org/10.3390/ijms12074206, PMID: 21845073

Gunaratnam K, Vidal C, Gimble JM, Duque G. 2014. Mechanisms of palmitate-induced lipotoxicity in human osteoblasts. *Endocrinology* **155**:108–116. DOI: https://doi.org/10.1210/en.2013-1712, PMID: 24169557

Hanoun M, Zhang D, Mizoguchi T, Pinho S, Pierce H, Kunisaki Y, Lacombe J, Armstrong SA, Dührsen U, Frenette PS. 2014. Acute myelogenous leukemia-induced sympathetic neuropathy promotes malignancy in an altered hematopoietic stem cell niche. *Cell Stem Cell* **15**:365–375. DOI: https://doi.org/10.1016/j.stem.2014.06.020, PMID: 25017722

Hase H, Ando T, Eldeiry L, Brebene A, Peng Y, Liu L, Amano H, Davies TF, Sun L, Zaidi M, Abe E. 2006. Tnfα mediates the skeletal effects of thyroid-stimulating hormone. *PNAS* **103**:12849–12854. DOI: https://doi.org/10.1073/pnas.0600427103, PMID: 16908863

Hayashi M, Nakashima T, Taniguchi M, Kodama T, Kumanogoh A, Takayanagi H. 2012. Osteoprotection by semaphorin 3A. *Nature* **485**:69–74. DOI: https://doi.org/10.1038/nature11000, PMID: 22522930

Heemstra KA, van der Deure WM, Peeters RP, Hamdy NA, Stokkel MP, Corssmit EP, Romijn JA, Visser TJ, Smit JW. 2008. Thyroid hormone independent associations between serum TSH levels and indicators of bone turnover in cured patients with differentiated thyroid carcinoma. *European Journal of Endocrinology* **159**:69–76. DOI: https://doi.org/10.1530/EJE-08-0038, PMID: 18390987

Hilton MJ, Tu X, Wu X, Bai S, Zhao H, Kobayashi T, Kronenberg HM, Teitelbaum SL, Ross FP, Kopan R, Long F. 2008. Notch signaling maintains bone marrow mesenchymal progenitors by suppressing osteoblast differentiation. *Nature Medicine* **14**:306–314. DOI: https://doi.org/10.1038/nm1716, PMID: 18297083

Hinoi E, Gao N, Jung DY, Yadav V, Yoshizawa T, Myers MG, Chua SC, Kim JK, Kaestner KH, Karsenty G. 2008. The sympathetic tone mediates leptin's inhibition of insulin secretion by modulating osteocalcin bioactivity. *The Journal of Cell Biology* **183**:1235–1242. DOI: https://doi.org/10.1083/jcb.200809113, PMID: 19103808

Hong S-H, Koo J-W, Hwang JK, Hwang Y-C, Jeong I-K, Ahn KJ, Chung H-Y, Kim D-Y. 2013. Changes in serum osteocalcin are not associated with changes in glucose or insulin for osteoporotic patients treated with bisphosphonate. *Journal of Bone Metabolism* **20**:37–41. DOI: https://doi.org/10.11005/jbm.2013.20.1.37, PMID: 24524054

Hsu H, Lacey DL, Dunstan CR, Solovyev I, Colombero A, Timms E, Tan HL, Elliott G, Kelley MJ, Sarosi I, Wang L, Xia XZ, Elliott R, Chiu L, Black T, Scully S, Capparelli C, Morony S, Shimamoto G, Bass MB, et al. 1999. Tumor necrosis factor receptor family member RANK mediates osteoclast differentiation and activation induced by osteoprotegerin ligand. *PNAS* **96**:3540–3545. DOI: https://doi.org/10.1073/pnas.96.7.3540, PMID: 10097072

Huang JC, Sakata T, Pfleger LL, Bencsik M, Halloran BP, Bikle DD, Nissenson RA. 2004. Pth differentially regulates expression of RANKL and OPG. *Journal of Bone and Mineral Research* **19**:235–244. DOI: https://doi.org/10.1359/JBMR.0301226, PMID: 14969393

Huang J, Hsu Y-H, Mo C, Abreu E, Kiel DP, Bonewald LF, Brotto M, Karasik D. 2014. METTL21C is a potential pleiotropic gene for osteoporosis and sarcopenia acting through the modulation of the NF-κB signaling pathway. *Journal of Bone and Mineral Research* **29**:1531–1540. DOI: https://doi.org/10.1002/jbmr.2200, PMID: 24677265

Huntley R, Jensen E, Gopalakrishnan R, Mansky KC. 2019. Bone morphogenetic proteins: their role in regulating osteoclast differentiation. *Bone Reports* **10**:100207. DOI: https://doi.org/10.1016/j.bonr.2019.100207, PMID: 31193008

Iqbal J, Zaidi M. 2005. Molecular regulation of mechanotransduction. *Biochemical and Biophysical Research Communications* **328**:751–755. DOI: https://doi.org/10.1016/j.bbrc.2004.12.087, PMID: 15694410

Iqbal J, Sun L, Kumar TR, Blair HC, Zaidi M. 2006. Follicle-stimulating hormone stimulates TNF production from immune cells to enhance osteoblast and osteoclast formation. *PNAS* **103**:14925–14930. DOI: https://doi.org/10.1073/pnas.0606805103, PMID: 17003115

Iqbal J, Sun L, Zaidi M. 2009. Coupling bone degradation to formation. *Nature Medicine* **15**:729–731. DOI: https://doi.org/10.1038/nm0709-729, PMID: 19584858

Isaksson OG, Lindahl A, Nilsson A, Isgaard J. 1987. Mechanism of the stimulatory effect of growth hormone on longitudinal bone growth. *Endocrine Reviews* **8**:426–438. DOI: https://doi.org/10.1210/edrv-8-4-426, PMID: 3319530

Isaksson OG, Ohlsson C, Nilsson A, Isgaard J, Lindahl A. 1991. Regulation of cartilage growth by growth hormone and insulin-like growth factor I. *Pediatric Nephrology* **5**:451–453. DOI: https://doi.org/10.1007/BF01453680, PMID: 1911121

Ishii M, Egen JG, Klauschen F, Meier-Schellersheim M, Saeki Y, Vacher J, Proia RL, Germain RN. 2009. Sphingosine-1-phosphate mobilizes osteoclast precursors and regulates bone homeostasis. *Nature* **458**:524–528. DOI: https://doi.org/10.1038/nature07713, PMID: 19204730

Ito I, Hanyu A, Wayama M, Goto N, Katsuno Y, Kawasaki S, Nakajima Y, Kajiro M, Komatsu Y, Fujimura A, Hirota R, Murayama A, Kimura K, Imamura T, Yanagisawa J. 2010. Estrogen inhibits transforming growth factor beta signaling by promoting smad2/3 degradation. *The Journal of Biological Chemistry* **285**:14747–14755. DOI: https://doi.org/10.1074/jbc.M109.093039, PMID: 20207742

Janes CH, Dickson ER, Okazaki R, Bonde S, McDonagh AF, Riggs BL. 1995. Role of hyperbilirubinemia in the impairment of osteoblast proliferation associated with cholestatic jaundice. *The Journal of Clinical Investigation* **95**:2581–2586. DOI: https://doi.org/10.1172/JCI117959, PMID: 7769100

Kajimura D, Lee HW, Riley KJ, Arteaga-Solis E, Ferron M, Zhou B, Clarke CJ, Hannun YA, DePinho RA, Guo XE, Mann JJ, Karsenty G. 2013. Adiponectin regulates bone mass via opposite central and peripheral mechanisms through foxo1. *Cell Metabolism* **17**:901–915. DOI: https://doi.org/10.1016/j.cmet.2013.04.009, PMID: 23684624

Kajimura D, Paone R, Mann JJ, Karsenty G. 2014. Foxo1 regulates dbh expression and the activity of the sympathetic nervous system in vivo. *Molecular Metabolism* **3**:770–777. DOI: https://doi.org/10.1016/j.molmet.2014.07.006, PMID: 25353004

Kaneki H, Guo R, Chen D, Yao Z, Schwarz EM, Zhang YE, Boyce BF, Xing L. 2006. Tumor necrosis factor promotes runx2 degradation through up-regulation of smurf1 and smurf2 in osteoblasts. *The Journal of Biological Chemistry* **281**:4326–4333. DOI: https://doi.org/10.1074/jbc.M509430200, PMID: 16373342

Karsak M, Cohen-Solal M, Freudenberg J, Ostertag A, Morieux C, Kornak U, Essig J, Erxlebe E, Bab I, Kubisch C, de Vernejoul M-C, Zimmer A. 2005. Cannabinoid receptor type 2 gene is associated with human osteoporosis. *Human Molecular Genetics* **14**:3389–3396. DOI: https://doi.org/10.1093/hmg/ddi370, PMID: 16204352

Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, Thomas SA, Frenette PS. 2006. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell* **124**:407–421. DOI: https://doi.org/10.1016/j.cell.2005.10.041, PMID: 16439213

Kerachian MA, Cournoyer D, Harvey EJ, Chow TY, Bégin LR, Nahal A, Séguin C. 2010. New insights into the pathogenesis of glucocorticoid-induced avascular necrosis: microarray analysis of gene expression in a rat model. *Arthritis Research & Therapy* **12**:R124. DOI: https://doi.org/10.1186/ar3062, PMID: 20579363

Khrimian L, Obri A, Ramos-Brossier M, Rousseaud A, Moriceau S, Nicot A-S, Mera P, Kosmidis S, Karnavas T, Saudou F, Gao X-B, Oury F, Kandel E, Karsenty G. 2017. Gpr158 mediates osteocalcin's regulation of cognition. *The Journal of Experimental Medicine* **214**:2859–2873. DOI: https://doi.org/10.1084/jem.20171320, PMID: 28851741

Kim DJ, Khang YH, Koh JM, Shong YK, Kim GS. 2006. Low normal TSH levels are associated with low bone mineral density in healthy postmenopausal women. *Clinical Endocrinology* **64**:86–90. DOI: https://doi.org/10.1111/j.1365-2265.2005.02422.x, PMID: 16402934

Kim B-J, Lee Y-S, Lee S-Y, Baek W-Y, Choi YJ, Moon SA, Lee SH, Kim J-E, Chang E-J, Kim E-Y, Yoon J, Kim S-W, Ryu SH, Lee S-K, Lorenzo JA, Ahn SH, Kim H, Lee K-U, Kim GS, Koh J-M. 2018. Osteoclast-secreted SLIT3 coordinates bone resorption and formation. *The Journal of Clinical Investigation* **128**:1429–1441. DOI: https://doi.org/10.1172/JCI91086, PMID: 29504949

Kim TY, Shoback DM, Black DM, Rogers SJ, Stewart L, Carter JT, Posselt AM, King NJ, Schafer AL. 2020a. Increases in PYY and uncoupling of bone turnover are associated with loss of bone mass after gastric bypass surgery. *Bone* **131**:115115. DOI: https://doi.org/10.1016/j.bone.2019.115115, PMID: 31689523

Kim SM, Taneja C, Perez-Pena H, Ryu V, Gumerova A, Li W, Ahmad N, Zhu LL, Liu P, Mathew M, Korkmaz F, Gera S, Sant D, Hadelia E, Ievleva K, Kuo TC, Miyashita H, Liu L, Tourkova I, Stanley S, et al. 2020b. Repurposing erectile dysfunction drugs tadalafil and vardenafil to increase bone mass. *PNAS* **117**:14386–14394. DOI: https://doi.org/10.1073/pnas.2000950117, PMID: 32513693

Kim SM, Yuen T, Iqbal J, Rubin MR, Zaidi M. 2020c. The NO-cgmp-PKG pathway in skeletal remodeling. *Annals of the New York Academy of Sciences* **1487**:21–30. DOI: https://doi.org/10.1111/nyas.14486, PMID: 32860248

Kim SM, Ryu V, Miyashita S, Korkmaz F, Lizneva D, Gera S, Latif R, Davies TF, Iqbal J, Yuen T, Zaidi M. 2021. Thyrotropin, hyperthyroidism, and bone mass. *The Journal of Clinical Endocrinology and Metabolism* **106**:e4809–e4821. DOI: https://doi.org/10.1210/clinem/dgab548, PMID: 34318885

Kleyer A, Scholtysek C, Bottesch E, Hillienhof U, Beyer C, Distler JH, Tuckermann JP, Schett G, Krönke G. 2012. Liver X receptors orchestrate osteoblast/osteoclast crosstalk and counteract pathologic bone loss. *Journal of Bone and Mineral Research* **27**:2442–2451. DOI: https://doi.org/10.1002/jbmr.1702, PMID: 22806960

Komatsu N, Okamoto K, Sawa S, Nakashima T, Oh-hora M, Kodama T, Tanaka S, Bluestone JA, Takayanagi H. 2014. Pathogenic conversion of Foxp3+ T cells into Th17 cells in autoimmune arthritis. *Nature Medicine* **20**:62–68. DOI: https://doi.org/10.1038/nm.3432, PMID: 24362934

Krishnan V, Bryant HU, Macdougald OA. 2006. Regulation of bone mass by Wnt signaling. *The Journal of Clinical Investigation* **116**:1202–1209. DOI: https://doi.org/10.1172/JCI28551, PMID: 16670761

Kusumbe AP, Ramasamy SK, Adams RH. 2014. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. *Nature* **507**:323–328. DOI: https://doi.org/10.1038/nature13145, PMID: 24646994

Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, Elliott R, Colombero A, Elliott G, Scully S, Hsu H, Sullivan J, Hawkins N, Davy E, Capparelli C, Eli A, Qian YX, Kaufman S, Sarosi I, Shalhoub V, et al. 1998. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* **93**:165–176. DOI: https://doi.org/10.1016/s0092-8674(00)81569-x, PMID: 9568710

Lawal RA, Zhou X, Batey K, Hoffman CM, Georger MA, Radtke F, Hilton MJ, Xing L, Frisch BJ, Calvi LM. 2017. The notch ligand jagged1 regulates the osteoblastic lineage by maintaining the osteoprogenitor pool. *Journal of Bone and Mineral Research* **32**:1320–1331. DOI: https://doi.org/10.1002/jbmr.3106, PMID: 28277610

Le PT, Liu H, Alabdulaaly L, Vegting Y, Calle IL, Gori F, Lanske B, Baron R, Rosen CJ. 2021. The role of zfp467 in mediating the pro-osteogenic and anti-adipogenic effects on bone and bone marrow niche. *Bone* **144**:115832. DOI: https://doi.org/10.1016/j.bone.2020.115832, PMID: 33359894

Li J-Y, D'Amelio P, Robinson J, Walker LD, Vaccaro C, Luo T, Tyagi AM, Yu M, Reott M, Sassi F, Buondonno I, Adams J, Weitzmann MN, Isaia GC, Pacifici R. 2015. Il-17A is increased in humans with primary hyperparathyroidism and mediates PTH-induced bone loss in mice. *Cell Metabolism* **22**:799–810. DOI: https://doi.org/10.1016/j.cmet.2015.09.012, PMID: 26456334

Li D, Liu J, Guo B, Liang C, Dang L, Lu C, He X, Cheung HY-S, Xu L, Lu C, He B, Liu B, Shaikh AB, Li F, Wang L, Yang Z, Au DW-T, Peng S, Zhang Z, Zhang B-T, et al. 2016. Osteoclast-derived exosomal mir-214-3p inhibits osteoblastic bone formation. *Nature Communications* **7**:10872. DOI: https://doi.org/10.1038/ncomms10872, PMID: 26947250

Li J-Y, Yu M, Tyagi AM, Vaccaro C, Hsu E, Adams J, Bellido T, Weitzmann MN, Pacifici R. 2019. Il-17 receptor signaling in osteoblasts/osteocytes mediates PTH-induced bone loss and enhances osteocytic RANKL production. *Journal of Bone and Mineral Research* **34**:349–360. DOI: https://doi.org/10.1002/jbmr.3600, PMID: 30399207

Liang B, Feng Y. 2012. The association of low bone mineral density with systemic inflammation in clinically stable COPD. *Endocrine* **42**:190–195. DOI: https://doi.org/10.1007/s12020-011-9583-x, PMID: 22198912

Liu X, Shimono K, Zhu L-L, Li J, Peng Y, Imam A, Iqbal J, Moonga S, Colaianni G, Su C, Lu Z, Iwamoto M, Pacifici M, Zallone A, Sun L, Zaidi M. 2009. Oxytocin deficiency impairs maternal skeletal remodeling. *Biochemical and Biophysical Research Communications* **388**:161–166. DOI: https://doi.org/10.1016/j.bbrc.2009.07.148, PMID: 19653998

Liu S, Cheng Y, Xu W, Bian Z. 2010. Protective effects of follicle-stimulating hormone inhibitor on alveolar bone loss resulting from experimental periapical lesions in ovariectomized rats. *Journal of Endodontics* **36**:658–663. DOI: https://doi.org/10.1016/j.joen.2010.01.011, PMID: 20307740

Liu P, Ji Y, Yuen T, Rendina-Ruedy E, DeMambro VE, Dhawan S, Abu-Amer W, Izadmehr S, Zhou B, Shin AC, Latif R, Thangeswaran P, Gupta A, Li J, Shnayder V, Robinson ST, Yu YE, Zhang X, Yang F, Lu P, et al. 2017. Blocking FSH induces thermogenic adipose tissue and reduces body fat. *Nature* **546**:107–112. DOI: https://doi.org/10.1038/nature22342, PMID: 28538730

Lu W, Wang W, Wang S, Feng Y, Liu K. 2016. Rosiglitazone promotes bone marrow adipogenesis to impair myelopoiesis under stress. *PLOS ONE* **11**:e0149543. DOI: https://doi.org/10.1371/journal.pone.0149543, PMID: 26895498

Luegmayr E, Glantschnig H, Wesolowski GA, Gentile MA, Fisher JE, Rodan GA, Reszka AA. 2004. Osteoclast formation, survival and morphology are highly dependent on exogenous cholesterol/lipoproteins. *Cell Death and Differentiation* **11 Suppl 1**:S108–S118. DOI: https://doi.org/10.1038/sj.cdd.4401399, PMID: 15017384

Luo J, Yang Z, Ma Y, Yue Z, Lin H, Qu G, Huang J, Dai W, Li C, Zheng C, Xu L, Chen H, Wang J, Li D, Siwko S, Penninger JM, Ning G, Xiao J, Liu M. 2016. LGR4 is a receptor for RANKL and negatively regulates osteoclast differentiation and bone resorption. *Nature Medicine* **22**:539–546. DOI: https://doi.org/10.1038/nm.4076, PMID: 27064449

Luo Z, Shang X, Zhang H, Wang G, Massey PA, Barton SR, Kevil CG, Dong Y. 2019. Notch signaling in osteogenesis, osteoclastogenesis, and angiogenesis. *The American Journal of Pathology* **189**:1495–1500. DOI: https://doi.org/10.1016/j.ajpath.2019.05.005, PMID: 31345466

Lupu F, Terwilliger JD, Lee K, Segre GV, Efstratiadis A. 2001. Roles of growth hormone and insulin-like growth factor 1 in mouse postnatal growth. *Developmental Biology* **229**:141–162. DOI: https://doi.org/10.1006/dbio.2000.9975, PMID: 11133160

Ma Z, Deng C, Hu W, Zhou J, Fan C, Di S, Liu D, Yang Y, Wang D. 2017. Liver X receptors and their agonists: targeting for cholesterol homeostasis and cardiovascular diseases. *Current Issues in Molecular Biology* **22**:41–64. DOI: https://doi.org/10.21775/cimb.022.041, PMID: 27669666

MacDonald BT, Tamai K, He X. 2009. Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Developmental Cell* **17**:9–26. DOI: https://doi.org/10.1016/j.devcel.2009.06.016, PMID: 19619488

Manolagas SC. 2010. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocrine Reviews* **31**:266–300. DOI: https://doi.org/10.1210/er.2009-0024, PMID: 20051526

Martini G, Gennari L, De Paola V, Pilli T, Salvadori S, Merlotti D, Valleggi F, Campagna S, Franci B, Avanzati A, Nuti R, Pacini F. 2008. The effects of recombinant TSH on bone turnover markers and serum osteoprotegerin and RANKL levels. *Thyroid* **18**:455–460. DOI: https://doi.org/10.1089/thy.2007.0166, PMID: 18399769

Matic I, Antunovic M, Brkic S, Josipovic P, Mihalic KC, Karlak I, Ivkovic A, Marijanovic I. 2016a. Expression of OCT-4 and SOX-2 in bone marrow-derived human mesenchymal stem cells during osteogenic differentiation. *Open Access Macedonian Journal of Medical Sciences* **4**:9–16. DOI: https://doi.org/10.3889/oamjms.2016.008, PMID: 27275321

Matic I, Matthews BG, Wang X, Dyment NA, Worthley DL, Rowe DW, Grcevic D, Kalajzic I. 2016b. Quiescent bone lining cells are a major source of osteoblasts during adulthood. *Stem Cells* **34**:2930–2942. DOI: https://doi.org/10.1002/stem.2474, PMID: 27507737

Matsushita M, Hasegawa S, Kitoh H, Mori K, Ohkawara B, Yasoda A, Masuda A, Ishiguro N, Ohno K. 2015. Meclozine promotes longitudinal skeletal growth in transgenic mice with achondroplasia carrying a gain-of-function mutation in the FGFR3 gene. *Endocrinology* **156**:548–554. DOI: https://doi.org/10.1210/en.2014-1914, PMID: 25456072

McClung MR, Lewiecki EM, Cohen SB, Bolognese MA, Woodson GC, Moffett AH, Peacock M, Miller PD, Lederman SN, Chesnut CH, Lain D, Kivitz AJ, Holloway DL, Zhang C, Peterson MC, Bekker PJ, AMG 162 Bone Loss Study Group. 2006. Denosumab in postmenopausal women with low bone mineral density. *The New England Journal of Medicine* **354**:821–831. DOI: https://doi.org/10.1056/NEJMoa044459, PMID: 16495394

McPherron AC, Lawler AM, Lee SJ. 1997. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature* **387**:83–90. DOI: https://doi.org/10.1038/387083a0, PMID: 9139826

McSheehy PM, Chambers TJ. 1986. Osteoblast-like cells in the presence of parathyroid hormone release soluble factor that stimulates osteoclastic bone resorption. *Endocrinology* **119**:1654–1659. DOI: https://doi.org/10.1210/endo-119-4-1654, PMID: 3463505

Méndez-Ferrer S, Lucas D, Battista M, Frenette PS. 2008. Haematopoietic stem cell release is regulated by circadian oscillations. *Nature* **452**:442–447. DOI: https://doi.org/10.1038/nature06685, PMID: 18256599

Méndez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, Scadden DT, Ma'ayan A, Enikolopov GN, Frenette PS. 2010. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. *Nature* **466**:829–834. DOI: https://doi.org/10.1038/nature09262, PMID: 20703299

Mera P, Laue K, Ferron M, Confavreux C, Wei J, Galán-Díez M, Lacampagne A, Mitchell SJ, Mattison JA, Chen Y, Bacchetta J, Szulc P, Kitsis RN, de Cabo R, Friedman RA, Torsitano C, McGraw TE, Puchowicz M, Kurland I, Karsenty G. 2016a. Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. *Cell Metabolism* **23**:1078–1092. DOI: https://doi.org/10.1016/j.cmet.2016.05.004, PMID: 27304508

Mera P, Laue K, Wei J, Berger JM, Karsenty G. 2016b. Osteocalcin is necessary and sufficient to maintain muscle mass in older mice. *Molecular Metabolism* **5**:1042–1047. DOI: https://doi.org/10.1016/j.molmet.2016.07.002, PMID: 27689017

Møller AMJ, Delaissé J-M, Olesen JB, Madsen JS, Canto LM, Bechmann T, Rogatto SR, Søe K. 2020. Aging and menopause reprogram osteoclast precursors for aggressive bone resorption. *Bone Research* **8**:27. DOI: https://doi.org/10.1038/s41413-020-0102-7, PMID: 32637185

Morgan I, Coulombe JC, Larsen M, Liu Z, Ferguson VL, Kumar TR. 2022. VISIONS: FSH and bone microarchitecture in mice. *Molecular Reproduction and Development* **89**:315. DOI: https://doi.org/10.1002/mrd.23629, PMID: 35789511

Morris MS. 2007. The association between serum thyroid-stimulating hormone in its reference range and bone status in postmenopausal american women. *Bone* **40**:1128–1134. DOI: https://doi.org/10.1016/j.bone.2006.12.001, PMID: 17236836

Nakashima T, Hayashi M, Fukunaga T, Kurata K, Oh-Hora M, Feng JQ, Bonewald LF, Kodama T, Wutz A, Wagner EF, Penninger JM, Takayanagi H. 2011. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. *Nature Medicine* **17**:1231–1234. DOI: https://doi.org/10.1038/nm.2452, PMID: 21909105

Nakatani T, Sarraj B, Ohnishi M, Densmore MJ, Taguchi T, Goetz R, Mohammadi M, Lanske B, Razzaque MS. 2009. In vivo genetic evidence for klotho-dependent, fibroblast growth factor 23 (fgf23) -mediated regulation of systemic phosphate homeostasis. *FASEB Journal* **23**:433–441. DOI: https://doi.org/10.1096/fj.08-114397, PMID: 18835926

Negishi-Koga T, Shinohara M, Komatsu N, Bito H, Kodama T, Friedel RH, Takayanagi H. 2011. Suppression of bone formation by osteoclastic expression of semaphorin 4D. *Nature Medicine* **17**:1473–1480. DOI: https://doi.org/10.1038/nm.2489, PMID: 22019888

Ninkovic M, Love S, Tom BDM, Bearcroft PWP, Alexander GJM, Compston JE. 2002. Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. *Journal of Hepatology* **37**:93–100. DOI: https://doi.org/10.1016/s0168-8278(02)00100-9, PMID: 12076867

Obri A, Khrimian L, Karsenty G, Oury F. 2018. Osteocalcin in the brain: from embryonic development to age-related decline in cognition. *Nature Reviews. Endocrinology* **14**:174–182. DOI: https://doi.org/10.1038/nrendo.2017.181, PMID: 29376523

Ofek O, Karsak M, Leclerc N, Fogel M, Frenkel B, Wright K, Tam J, Attar-Namdar M, Kram V, Shohami E, Mechoulam R, Zimmer A, Bab I. 2006. Peripheral cannabinoid receptor, CB2, regulates bone mass. *PNAS* **103**:696–701. DOI: https://doi.org/10.1073/pnas.0504187103, PMID: 16407142

Ohlsson C, Bengtsson BA, Isaksson OG, Andreassen TT, Slootweg MC. 1998. Growth hormone and bone. *Endocrine Reviews* **19**:55–79. DOI: https://doi.org/10.1210/edrv.19.1.0324, PMID: 9494780

Ohlsson C, Mohan S, Sjögren K, Tivesten A, Isgaard J, Isaksson O, Jansson J-O, Svensson J. 2009. The role of liver-derived insulin-like growth factor-I. *Endocrine Reviews* **30**:494–535. DOI: https://doi.org/10.1210/er.2009-0010, PMID: 19589948

Oishi Y, Manabe I. 2020. Organ system crosstalk in cardiometabolic disease in the age of multimorbidity. *Frontiers in Cardiovascular Medicine* **7**:64. DOI: https://doi.org/10.3389/fcvm.2020.00064, PMID: 32411724

Otero K, Shinohara M, Zhao H, Cella M, Gilfillan S, Colucci A, Faccio R, Ross FP, Teitelbaum SL, Takayanagi H, Colonna M. 2012. Trem2 and β-catenin regulate bone homeostasis by controlling the rate of osteoclastogenesis. *Journal of Immunology* **188**:2612–2621. DOI: https://doi.org/10.4049/jimmunol.1102836, PMID: 22312126

Oury F, Khrimian L, Denny CA, Gardin A, Chamouni A, Goeden N, Huang Y, Lee H, Srinivas P, Gao X-B, Suyama S, Langer T, Mann JJ, Horvath TL, Bonnin A, Karsenty G. 2013. Maternal and offspring pools of osteocalcin influence brain development and functions. *Cell* **155**:228–241. DOI: https://doi.org/10.1016/j.cell.2013.08.042, PMID: 24074871

Pállinger E, Csaba G. 2008. A hormone map of human immune cells showing the presence of adrenocorticotropic hormone, triiodothyronine and endorphin in immunophenotyped white blood cells. *Immunology* **123**:584–589. DOI: https://doi.org/10.1111/j.1365-2567.2007.02731.x, PMID: 18005034

Pederson L, Ruan M, Westendorf JJ, Khosla S, Oursler MJ. 2008. Regulation of bone formation by osteoclasts involves wnt/BMP signaling and the chemokine sphingosine-1-phosphate. *PNAS* **105**:20764–20769. DOI: https://doi.org/10.1073/pnas.0805133106, PMID: 19075223

Pfeilschifter J, Chenu C, Bird A, Mundy GR, Roodman GD. 1989. Interleukin-1 and tumor necrosis factor stimulate the formation of human osteoclastlike cells in vitro. *Journal of Bone and Mineral Research* **4**:113–118. DOI: https://doi.org/10.1002/jbmr.5650040116, PMID: 2785743

Pi Min, Chen L, Huang M-Z, Zhu W, Ringhofer B, Luo J, Christenson L, Li B, Zhang J, Jackson PD, Faber P, Brunden KR, Harrington JJ, Quarles LD. 2008. Gprc6A null mice exhibit osteopenia, feminization and metabolic syndrome. *PLOS ONE* **3**:e3858. DOI: https://doi.org/10.1371/journal.pone.0003858, PMID: 19050760

Pi M., Wu Y, Quarles LD. 2011. Gprc6A mediates responses to osteocalcin in β-cells in vitro and pancreas in vivo. *Journal of Bone and Mineral Research* **26**:1680–1683. DOI: https://doi.org/10.1002/jbmr.390, PMID: 21425331

Pierce JL, Begun DL, Westendorf JJ, McGee-Lawrence ME. 2019. Defining osteoblast and adipocyte lineages in the bone marrow. *Bone* **118**:2–7. DOI: https://doi.org/10.1016/j.bone.2018.05.019, PMID: 29782940

Qiang Y-W, Chen Y, Stephens O, Brown N, Chen B, Epstein J, Barlogie B, Shaughnessy JD. 2008. Myeloma-derived dickkopf-1 disrupts wnt-regulated osteoprotegerin and RANKL production by osteoblasts: a potential mechanism underlying osteolytic bone lesions in multiple myeloma. *Blood* **112**:196–207. DOI: https://doi.org/10.1182/blood-2008-01-132134, PMID: 18305214

Qin W, Sun L, Cao J, Peng Y, Collier L, Wu Y, Creasey G, Li J, Qin Y, Jarvis J, Bauman WA, Zaidi M, Cardozo C. 2013. The central nervous system (CNS)-independent anti-bone-resorptive activity of muscle contraction and the underlying molecular and cellular signatures. *The Journal of Biological Chemistry* **288**:13511–13521. DOI: https://doi.org/10.1074/jbc.M113.454892, PMID: 23530032

Qin Y, Peng Y, Zhao W, Pan J, Ksiezak-Reding H, Cardozo C, Wu Y, Divieti Pajevic P, Bonewald LF, Bauman WA, Qin W. 2017. Myostatin inhibits osteoblastic differentiation by suppressing osteocyte-derived exosomal microrna-218: A novel mechanism in muscle-bone communication. *The Journal of Biological Chemistry* **292**:11021–11033. DOI: https://doi.org/10.1074/jbc.M116.770941, PMID: 28465350

Quach JM, Walker EC, Allan E, Solano M, Yokoyama A, Kato S, Sims NA, Gillespie MT, Martin TJ. 2011. Zinc finger protein 467 is a novel regulator of osteoblast and adipocyte commitment. *The Journal of Biological Chemistry* **286**:4186–4198. DOI: https://doi.org/10.1074/jbc.M110.178251, PMID: 21123171

Ramajayam G, Vignesh RC, Karthikeyan S, Kumar KS, Karthikeyan GD, Veni S, Sridhar M, Arunakaran J, Aruldhas MM, Srinivasan N. 2012. Regulation of insulin-like growth factors and their binding proteins by

thyroid stimulating hormone in human osteoblast-like (saos2) cells. *Molecular and Cellular Biochemistry* **368**:77–88. DOI: https://doi.org/10.1007/s11010-012-1345-4, PMID: 22673962

Randolph JF Jr, Sowers M, Gold EB, Mohr BA, Luborsky J, Santoro N, McConnell DS, Finkelstein JS, Korenman SG, Matthews KA, Sternfeld B, Lasley BL. 2003. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. *The Journal of Clinical Endocrinology and Metabolism* **88**:1516–1522. DOI: https://doi.org/10.1210/jc.2002-020777, PMID: 12679432

Rankin EB, Wu C, Khatri R, Wilson TLS, Andersen R, Araldi E, Rankin AL, Yuan J, Kuo CJ, Schipani E, Giaccia AJ. 2012. The HIF signaling pathway in osteoblasts directly modulates erythropoiesis through the production of EPO. *Cell* **149**:63–74. DOI: https://doi.org/10.1016/j.cell.2012.01.051, PMID: 22464323

Rauner M, Sipos W, Pietschmann P. 2008. Age-dependent wnt gene expression in bone and during the course of osteoblast differentiation. *Age* **30**:273–282. DOI: https://doi.org/10.1007/s11357-008-9069-9, PMID: 19424851

Reid IR, Lucas J, Wattie D, Horne A, Bolland M, Gamble GD, Davidson JS, Grey AB. 2005. Effects of a beta-blocker on bone turnover in normal postmenopausal women: a randomized controlled trial. *The Journal of Clinical Endocrinology and Metabolism* **90**:5212–5216. DOI: https://doi.org/10.1210/jc.2005-0573, PMID: 15998769

Rendina D, Gianfrancesco F, De Filippo G, Merlotti D, Esposito T, Mingione A, Nuti R, Strazzullo P, Mossetti G, Gennari L. 2010. Fshr gene polymorphisms influence bone mineral density and bone turnover in postmenopausal women. *European Journal of Endocrinology* **163**:165–172. DOI: https://doi.org/10.1530/EJE-10-0043, PMID: 20335500

Rivadeneira F, Styrkársdottir U, Estrada K, Halldórsson BV, Hsu Y-H, Richards JB, Zillikens MC, Kavvoura FK, Amin N, Aulchenko YS, Cupples LA, Deloukas P, Demissie S, Grundberg E, Hofman A, Kong A, Karasik D, van Meurs JB, Oostra B, Pastinen T, et al. 2009. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. *Nature Genetics* **41**:1199–1206. DOI: https://doi.org/10.1038/ng.446, PMID: 19801982

Robinson LJ, Tourkova I, Wang Y, Sharrow AC, Landau MS, Yaroslavskiy BB, Sun L, Zaidi M, Blair HC. 2010. FSH-receptor isoforms and FSH-dependent gene transcription in human monocytes and osteoclasts. *Biochemical and Biophysical Research Communications* **394**:12–17. DOI: https://doi.org/10.1016/j.bbrc.2010.02.112, PMID: 20171950

Roman-Garcia P, Quiros-Gonzalez I, Mottram L, Lieben L, Sharan K, Wangwiwatsin A, Tubio J, Lewis K, Wilkinson D, Santhanam B, Sarper N, Clare S, Vassiliou GS, Velagapudi VR, Dougan G, Yadav VK. 2014. Vitamin B_{12}-dependent taurine synthesis regulates growth and bone mass. *The Journal of Clinical Investigation* **124**:2988–3002. DOI: https://doi.org/10.1172/JCI72606, PMID: 24911144

Ruiz-Gaspà S, Martinez-Ferrer A, Guañabens N, Dubreuil M, Peris P, Enjuanes A, Martinez de Osaba MJ, Alvarez L, Monegal A, Combalia A, Parés A. 2011. Effects of bilirubin and sera from jaundiced patients on osteoblasts: contribution to the development of osteoporosis in liver diseases. *Hepatology* **54**:2104–2113. DOI: https://doi.org/10.1002/hep.24605, PMID: 21837749

Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. 2017. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *The New England Journal of Medicine* **377**:1417–1427. DOI: https://doi.org/10.1056/NEJMoa1708322, PMID: 28892457

Sadeghi F, Vahednia E, Naderi Meshkin H, Kerachian MA. 2020. The effect of adrenocorticotropic hormone on alpha-2-macroglobulin in osteoblasts derived from human mesenchymal stem cells. *Journal of Cellular and Molecular Medicine* **24**:4784–4790. DOI: https://doi.org/10.1111/jcmm.15152, PMID: 32163666

Salazar VS, Gamer LW, Rosen V. 2016. BMP signalling in skeletal development, disease and repair. *Nature Reviews. Endocrinology* **12**:203–221. DOI: https://doi.org/10.1038/nrendo.2016.12, PMID: 26893264

Sampath TK, Simic P, Sendak R, Draca N, Bowe AE, O'Brien S, Schiavi SC, McPherson JM, Vukicevic S. 2007. Thyroid-stimulating hormone restores bone volume, microarchitecture, and strength in aged ovariectomized rats. *Journal of Bone and Mineral Research* **22**:849–859. DOI: https://doi.org/10.1359/jbmr.070302, PMID: 17352644

Sato S, Hanada R, Kimura A, Abe T, Matsumoto T, Iwasaki M, Inose H, Ida T, Mieda M, Takeuchi Y, Fukumoto S, Fujita T, Kato S, Kangawa K, Kojima M, Shinomiya K, Takeda S. 2007. Central control of bone remodeling by neuromedin U. *Nature Medicine* **13**:1234–1240. DOI: https://doi.org/10.1038/nm1640, PMID: 17873881

Schipani E, Maes C, Carmeliet G, Semenza GL. 2009. Regulation of osteogenesis-angiogenesis coupling by hifs and VEGF. *Journal of Bone and Mineral Research* **24**:1347–1353. DOI: https://doi.org/10.1359/jbmr.090602, PMID: 19558314

Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. 2004. Use of beta-blockers and risk of fractures. *JAMA* **292**:1326–1332. DOI: https://doi.org/10.1001/jama.292.11.1326, PMID: 15367554

Schroder EA, Harfmann BD, Zhang X, Srikuea R, England JH, Hodge BA, Wen Y, Riley LA, Yu Q, Christie A, Smith JD, Seward T, Wolf Horrell EM, Mula J, Peterson CA, Butterfield TA, Esser KA. 2015. Intrinsic muscle clock is necessary for musculoskeletal health. *The Journal of Physiology* **593**:5387–5404. DOI: https://doi.org/10.1113/JP271436, PMID: 26486627

Seriwatanachai D, Thongchote K, Charoenphandhu N, Pandaranandaka J, Tudpor K, Teerapornpuntakit J, Suthiphongchai T, Krishnamra N. 2008. Prolactin directly enhances bone turnover by raising osteoblast-expressed receptor activator of nuclear factor kappaB ligand/osteoprotegerin ratio. *Bone* **42**:535–546. DOI: https://doi.org/10.1016/j.bone.2007.11.008, PMID: 18166509

Shah TA, Rogers MB. 2018. Unanswered questions regarding sex and BMP/TGF-β signaling. *Journal of Developmental Biology* **6**:14. DOI: https://doi.org/10.3390/jdb6020014, PMID: 29914150

Shen R, Chen M, Wang Y-J, Kaneki H, Xing L, O'keefe RJ, Chen D. 2006. Smad6 interacts with Runx2 and mediates Smad ubiquitin regulatory factor 1-induced Runx2 degradation. *The Journal of Biological Chemistry* **281**:3569–3576. DOI: https://doi.org/10.1074/jbc.M506761200, PMID: 16299379

Shi YC, Baldock PA. 2012. Central and peripheral mechanisms of the NPY system in the regulation of bone and adipose tissue. *Bone* **50**:430–436. DOI: https://doi.org/10.1016/j.bone.2011.10.001, PMID: 22008645

Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T. 2001. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *PNAS* **98**:6500–6505. DOI: https://doi.org/10.1073/pnas.101545198, PMID: 11344269

Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, Fukumoto S, Tomizuka K, Yamashita T. 2004. Targeted ablation of FGF23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *The Journal of Clinical Investigation* **113**:561–568. DOI: https://doi.org/10.1172/JCI19081, PMID: 14966565

Shooshtarizadeh P, Helness A, Vadnais C, Brouwer N, Beauchemin H, Chen R, Bagci H, Staal FJT, Coté J-F, Möröy T. 2019. Gfi1b regulates the level of wnt/β-catenin signaling in hematopoietic stem cells and megakaryocytes. *Nature Communications* **10**:1270. DOI: https://doi.org/10.1038/s41467-019-09273-z, PMID: 30894540

Simonet WS, Lacey DL, Dunstan CR, Kelley M, Chang MS, Lüthy R, Nguyen HQ, Wooden S, Bennett L, Boone T, Shimamoto G, DeRose M, Elliott R, Colombero A, Tan HL, Trail G, Sullivan J, Davy E, Bucay N, Renshaw-Gegg L, et al. 1997. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* **89**:309–319. DOI: https://doi.org/10.1016/s0092-8674(00)80209-3, PMID: 9108485

Sjögren K, Liu JL, Blad K, Skrtic S, Vidal O, Wallenius V, LeRoith D, Törnell J, Isaksson OG, Jansson JO, Ohlsson C. 1999. Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. *PNAS* **96**:7088–7092. DOI: https://doi.org/10.1073/pnas.96.12.7088, PMID: 10359843

Sowers M, Eyre D, Hollis BW, Randolph JF, Shapiro B, Jannausch ML, Crutchfield M. 1995. Biochemical markers of bone turnover in lactating and nonlactating postpartum women. *The Journal of Clinical Endocrinology and Metabolism* **80**:2210–2216. DOI: https://doi.org/10.1210/jcem.80.7.7608281, PMID: 7608281

Sowers MR, Greendale GA, Bondarenko I, Finkelstein JS, Cauley JA, Neer RM, Ettinger B. 2003. Endogenous hormones and bone turnover markers in pre- and perimenopausal women: Swan. *Osteoporosis International* **14**:191–197. DOI: https://doi.org/10.1007/s00198-002-1329-4, PMID: 12730778

Stachnik A, Yuen T, Iqbal J, Sgobba M, Gupta Y, Lu P, Colaianni G, Ji Y, Zhu LL, Kim SM, Li J, Liu P, Izadmehr S, Sangodkar J, Scherer T, Mujtaba S, Galsky M, Gomez J, Epstein S, Buettner C, et al. 2014. Repurposing of bisphosphonates for the prevention and therapy of nonsmall cell lung and breast cancer. *PNAS* **111**:17995–18000. DOI: https://doi.org/10.1073/pnas.1421422111, PMID: 25453078

Stratikopoulos E, Szabolcs M, Dragatsis I, Klinakis A, Efstratiadis A. 2008. The hormonal action of IGF1 in postnatal mouse growth. *PNAS* **105**:19378–19383. DOI: https://doi.org/10.1073/pnas.0809223105, PMID: 19033454

Suchacki KJ, Cawthorn WP, Rosen CJ. 2016. Bone marrow adipose tissue: formation, function and regulation. *Current Opinion in Pharmacology* **28**:50–56. DOI: https://doi.org/10.1016/j.coph.2016.03.001, PMID: 27022859

Sun L, Blair HC, Peng Y, Zaidi N, Adebanjo OA, Wu XB, Wu XY, Iqbal J, Epstein S, Abe E, Moonga BS, Zaidi M. 2005. Calcineurin regulates bone formation by the osteoblast. *PNAS* **102**:17130–17135. DOI: https://doi.org/10.1073/pnas.0508480102, PMID: 16286645

Sun L, Peng Y, Sharrow AC, Iqbal J, Zhang Z, Papachristou DJ, Zaidi S, Zhu L-L, Yaroslavskiy BB, Zhou H, Zallone A, Sairam MR, Kumar TR, Bo W, Braun J, Cardoso-Landa L, Schaffler MB, Moonga BS, Blair HC, Zaidi M. 2006. Fsh directly regulates bone mass. *Cell* **125**:247–260. DOI: https://doi.org/10.1016/j.cell.2006.01.051, PMID: 16630814

Sun L, Peng Y, Zaidi N, Zhu LL, Iqbal J, Yamoah K, Wang X, Liu P, Abe E, Moonga BS, Epstein S, Zaidi M. 2007. Evidence that calcineurin is required for the genesis of bone-resorbing osteoclasts. *American Journal of Physiology. Renal Physiology* **292**:F285–F291. DOI: https://doi.org/10.1152/ajprenal.00415.2005, PMID: 16968888

Sun L, Vukicevic S, Baliram R, Yang G, Sendak R, McPherson J, Zhu LL, Iqbal J, Latif R, Natrajan A, Arabi A, Yamoah K, Moonga BS, Gabet Y, Davies TF, Bab I, Abe E, Sampath K, Zaidi M. 2008. Intermittent recombinant TSH injections prevent ovariectomy-induced bone loss. *PNAS* **105**:4289–4294. DOI: https://doi.org/10.1073/pnas.0712395105, PMID: 18332426

Sun L, Zhu LL, Lu P, Yuen T, Li J, Ma R, Baliram R, Moonga SS, Liu P, Zallone A, New MI, Davies TF, Zaidi M. 2013. Genetic confirmation for a central role for tnfα in the direct action of thyroid stimulating hormone on the skeleton. *PNAS* **110**:9891–9896. DOI: https://doi.org/10.1073/pnas.1308336110, PMID: 23716650

Sun L, Tamma R, Yuen T, Colaianni G, Ji Y, Cuscito C, Bailey J, Dhawan S, Lu P, Calvano CD, Zhu LL, Zambonin CG, Di Benedetto A, Stachnik A, Liu P, Grano M, Colucci S, Davies TF, New MI, Zallone A, et al. 2016. Functions of vasopressin and oxytocin in bone mass regulation. *PNAS* **113**:164–169. DOI: https://doi.org/10.1073/pnas.1523762113, PMID: 26699482

Sun L, Lizneva D, Ji Y, Colaianni G, Hadelia E, Gumerova A, Ievleva K, Kuo TC, Korkmaz F, Ryu V, Rahimova A, Gera S, Taneja C, Khan A, Ahmad N, Tamma R, Bian Z, Zallone A, Kim SM, New MI, et al. 2019. Oxytocin regulates body composition. *PNAS* **116**:26808–26815. DOI: https://doi.org/10.1073/pnas.1913611116, PMID: 31843930

Takayanagi H. 2007. Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. *Nature Reviews. Immunology* **7**:292–304. DOI: https://doi.org/10.1038/nri2062, PMID: 17380158

Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, Armstrong D, Ducy P, Karsenty G. 2002. Leptin regulates bone formation via the sympathetic nervous system. *Cell* **111**:305–317. DOI: https://doi.org/10.1016/s0092-8674(02)01049-8, PMID: 12419242

Tam J, Trembovler V, Di Marzo V, Petrosino S, Leo G, Alexandrovich A, Regev E, Casap N, Shteyer A, Ledent C, Karsak M, Zimmer A, Mechoulam R, Yirmiya R, Shohami E, Bab I. 2008. The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. *FASEB Journal* **22**:285–294. DOI: https://doi.org/10.1096/fj.06-7957com, PMID: 17704191

Tamma R, Colaianni G, Zhu L, DiBenedetto A, Greco G, Montemurro G, Patano N, Strippoli M, Vergari R, Mancini L, Colucci S, Grano M, Faccio R, Liu X, Li J, Usmani S, Bachar M, Bab I, Nishimori K, Young LJ, et al. 2009. Oxytocin is an anabolic bone hormone. *PNAS* **106**:7149–7154. DOI: https://doi.org/10.1073/pnas.0901890106, PMID: 19369205

Tamma R, Sun L, Cuscito C, Lu P, Corcelli M, Li J, Colaianni G, Moonga SS, Di Benedetto A, Grano M, Colucci S, Yuen T, New MI, Zallone A, Zaidi M. 2013. Regulation of bone remodeling by vasopressin explains the bone loss in hyponatremia. *PNAS* **110**:18644–18649. DOI: https://doi.org/10.1073/pnas.1318257110, PMID: 24167258

Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X. 2009. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nature Medicine* **15**:757–765. DOI: https://doi.org/10.1038/nm.1979, PMID: 19584867

Tencerova M, Kassem M. 2016. The bone marrow-derived stromal cells: commitment and regulation of adipogenesis. *Frontiers in Endocrinology* **7**:127. DOI: https://doi.org/10.3389/fendo.2016.00127, PMID: 27708616

Thrailkill KM, Jo CH, Cockrell GE, Moreau CS, Lumpkin CK, Fowlkes JL. 2012. Determinants of undercarboxylated and carboxylated osteocalcin concentrations in type 1 diabetes. *Osteoporosis International* **23**:1799–1806. DOI: https://doi.org/10.1007/s00198-011-1807-7, PMID: 22068385

Tsuchida A, Yamauchi T, Takekawa S, Hada Y, Ito Y, Maki T, Kadowaki T. 2005. Peroxisome proliferator-activated receptor (PPAR) alpha activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARalpha, PPARgamma, and their combination. *Diabetes* **54**:3358–3370. DOI: https://doi.org/10.2337/diabetes.54.12.3358, PMID: 16306350

van der Deure WM, Uitterlinden AG, Hofman A, Rivadeneira F, Pols HAP, Peeters RP, Visser TJ. 2008. Effects of serum TSH and FT4 levels and the TSHR-asp727glu polymorphism on bone: the rotterdam study. *Clinical Endocrinology* **68**:175–181. DOI: https://doi.org/10.1111/j.1365-2265.2007.03016.x, PMID: 17803697

Veldhuis-Vlug AG, Woods GN, Sigurdsson S, Ewing SK, Le PT, Hue TF, Vittinghoff E, Xu K, Gudnason V, Sigurdsson G, Kado DM, Eiriksdottir G, Harris T, Schafer AL, Li X, Zaidi M, Rosen CJ, Schwartz AV. 2021. Serum FSH is associated with BMD, bone marrow adiposity, and body composition in the AGES-Reykjavik study of older adults. *The Journal of Clinical Endocrinology and Metabolism* **106**:e1156–e1169. DOI: https://doi.org/10.1210/clinem/dgaa922, PMID: 33326040

Vignaux G, Ndong JD, Perrien DS, Elefteriou F. 2015. Inner ear vestibular signals regulate bone remodeling via the sympathetic nervous system. *Journal of Bone and Mineral Research* **30**:1103–1111. DOI: https://doi.org/10.1002/jbmr.2426, PMID: 25491117

Wallner C, Jaurich H, Wagner JM, Becerikli M, Harati K, Dadras M, Lehnhardt M, Behr B. 2017. Inhibition of GDF8 (myostatin) accelerates bone regeneration in diabetes mellitus type 2. *Scientific Reports* **7**:9878. DOI: https://doi.org/10.1038/s41598-017-10404-z, PMID: 28852138

Wan M, Cao X. 2005. Bmp signaling in skeletal development. *Biochemical and Biophysical Research Communications* **328**:651–657. DOI: https://doi.org/10.1016/j.bbrc.2004.11.067, PMID: 15694398

Wang Y, Wan C, Deng L, Liu X, Cao X, Gilbert SR, Bouxsein ML, Faugere M-C, Guldberg RE, Gerstenfeld LC, Haase VH, Johnson RS, Schipani E, Clemens TL. 2007. The hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development. *The Journal of Clinical Investigation* **117**:1616–1626. DOI: https://doi.org/10.1172/JCI31581, PMID: 17549257

Wang J, Zhang W, Yu C, Zhang X, Zhang H, Guan Q, Zhao J, Xu J. 2015. Follicle-Stimulating hormone increases the risk of postmenopausal osteoporosis by stimulating osteoclast differentiation. *PLOS ONE* **10**:e0134986. DOI: https://doi.org/10.1371/journal.pone.0134986, PMID: 26241313

Wang CY, Xu Y, Traeger L, Dogan DY, Xiao X, Steinbicker AU, Babitt JL. 2020. Erythroferrone lowers hepcidin by sequestering BMP2/6 heterodimer from binding to the BMP type I receptor ALK3. *Blood* **135**:453–456. DOI: https://doi.org/10.1182/blood.2019002620, PMID: 31800957

Weber JM, Calvi LM. 2010. Notch signaling and the bone marrow hematopoietic stem cell niche. *Bone* **46**:281–285. DOI: https://doi.org/10.1016/j.bone.2009.08.007, PMID: 19679213

Wei J, Ferron M, Clarke CJ, Hannun YA, Jiang H, Blaner WS, Karsenty G. 2014a. Bone-specific insulin resistance disrupts whole-body glucose homeostasis via decreased osteocalcin activation. *The Journal of Clinical Investigation* **124**:1–13. DOI: https://doi.org/10.1172/JCI72323, PMID: 24642469

Wei J, Hanna T, Suda N, Karsenty G, Ducy P. 2014b. Osteocalcin promotes β-cell proliferation during development and adulthood through GPRC6A. *Diabetes* **63**:1021–1031. DOI: https://doi.org/10.2337/db13-0887, PMID: 24009262

Wu X-B, Li Y, Schneider A, Yu W, Rajendren G, Iqbal J, Yamamoto M, Alam M, Brunet LJ, Blair HC, Zaidi M, Abe E. 2003. Impaired osteoblastic differentiation, reduced bone formation, and severe osteoporosis in

noggin-overexpressing mice. *The Journal of Clinical Investigation* **112**:924–934. DOI: https://doi.org/10.1172/JCI15543, PMID: 12975477

Wu Y, Torchia J, Yao W, Lane NE, Lanier LL, Nakamura MC, Humphrey MB. 2007. Bone microenvironment specific roles of ITAM adapter signaling during bone remodeling induced by acute estrogen-deficiency. *PLOS ONE* **2**:e586. DOI: https://doi.org/10.1371/journal.pone.0000586, PMID: 17611621

Wu X-Y, Wu X-P, Xie H, Zhang H, Peng Y-Q, Yuan L-Q, Su X, Luo X-H, Liao E-Y. 2010. Age-Related changes in biochemical markers of bone turnover and gonadotropin levels and their relationship among Chinese adult women. *Osteoporosis International* **21**:275–285. DOI: https://doi.org/10.1007/s00198-009-0943-9, PMID: 19562242

Wu C, Rankin EB, Castellini L, Alcudia JF, LaGory EL, Andersen R, Rhodes SD, Wilson TLS, Mohammad KS, Castillo AB, Guise TA, Schipani E, Giaccia AJ. 2015. Oxygen-Sensing PhDs regulate bone homeostasis through the modulation of osteoprotegerin. *Genes & Development* **29**:817–831. DOI: https://doi.org/10.1101/gad.255000.114, PMID: 25846796

Wu M, Chen G, Li YP. 2016. Tgf-β and BMP signaling in osteoblast, skeletal development, and bone formation, homeostasis and disease. *Bone Research* **4**:16009. DOI: https://doi.org/10.1038/boneres.2016.9, PMID: 27563484

Wysolmerski JJ. 2002. The evolutionary origins of maternal calcium and bone metabolism during lactation. *Journal of Mammary Gland Biology and Neoplasia* **7**:267–276. DOI: https://doi.org/10.1023/a:1022800716196, PMID: 12751891

Xiong J., Onal M, Jilka RL, Weinstein RS, Manolagas SC, O'Brien CA. 2011. Matrix-embedded cells control osteoclast formation. *Nature Medicine* **17**:1235–1241. DOI: https://doi.org/10.1038/nm.2448, PMID: 21909103

Xiong J, Piemontese M, Onal M, Campbell J, Goellner JJ, Dusevich V, Bonewald L, Manolagas SC, O'Brien CA. 2015. Osteocytes, not osteoblasts or lining cells, are the main source of the RANKL required for osteoclast formation in remodeling bone. *PLOS ONE* **10**:e0138189. DOI: https://doi.org/10.1371/journal.pone.0138189, PMID: 26393791

Xu Z-R, Wang A-H, Wu X-P, Zhang H, Sheng Z-F, Wu X-Y, Xie H, Luo X-H, Liao E-Y. 2009. Relationship of age-related concentrations of serum FSH and LH with bone mineral density, prevalence of osteoporosis in native Chinese women. *Clinica Chimica Acta; International Journal of Clinical Chemistry* **400**:8–13. DOI: https://doi.org/10.1016/j.cca.2008.09.027, PMID: 18930719

Yakar S, Liu JL, Stannard B, Butler A, Accili D, Sauer B, LeRoith D. 1999. Normal growth and development in the absence of hepatic insulin-like growth factor I. *PNAS* **96**:7324–7329. DOI: https://doi.org/10.1073/pnas.96.13.7324, PMID: 10377413

Yakar S, Rosen CJ, Bouxsein ML, Sun H, Mejia W, Kawashima Y, Wu Y, Emerton K, Williams V, Jepsen K, Schaffler MB, Majeska RJ, Gavrilova O, Gutierrez M, Hwang D, Pennisi P, Frystyk J, Boisclair Y, Pintar J, Jasper H, et al. 2009. Serum complexes of insulin-like growth factor-1 modulate skeletal integrity and carbohydrate metabolism. *FASEB Journal* **23**:709–719. DOI: https://doi.org/10.1096/fj.08-118976, PMID: 18952711

Yamashita T, Murakami T, Otani S, Kuwajima M, Shima K. 1998. Leptin receptor signal transduction: obra and obrb of fa type. *Biochemical and Biophysical Research Communications* **246**:752–759. DOI: https://doi.org/10.1006/bbrc.1998.8689, PMID: 9618284

Yan Y, Tang D, Chen M, Huang J, Xie R, Jonason JH, Tan X, Hou W, Reynolds D, Hsu W, Harris SE, Puzas JE, Awad H, O'Keefe RJ, Boyce BF, Chen D. 2009. Axin2 controls bone remodeling through the beta-catenin-BMP signaling pathway in adult mice. *Journal of Cell Science* **122**:3566–3578. DOI: https://doi.org/10.1242/jcs.051904, PMID: 19737815

Yu W, Zhong L, Yao L, Wei Y, Gui T, Li Z, Kim H, Holdreith N, Jiang X, Tong W, Dyment N, Liu XS, Yang S, Choi Y, Ahn J, Qin L. 2021. Bone marrow adipogenic lineage precursors promote osteoclastogenesis in bone remodeling and pathologic bone loss. *The Journal of Clinical Investigation* **131**:e140214. DOI: https://doi.org/10.1172/JCI140214, PMID: 33206630

Yue R, Zhou BO, Shimada IS, Zhao Z, Morrison SJ. 2016. Leptin receptor promotes adipogenesis and reduces osteogenesis by regulating mesenchymal stromal cells in adult bone marrow. *Cell Stem Cell* **18**:782–796. DOI: https://doi.org/10.1016/j.stem.2016.02.015, PMID: 27053299

Yuen T, Stachnik A, Iqbal J, Sgobba M, Gupta Y, Lu P, Colaianni G, Ji Y, Zhu LL, Kim SM, Li J, Liu P, Izadmehr S, Sangodkar J, Bailey J, Latif Y, Mujtaba S, Epstein S, Davies TF, Bian Z, et al. 2014. Bisphosphonates inactivate human egfrs to exert antitumor actions. *PNAS* **111**:17989–17994. DOI: https://doi.org/10.1073/pnas.1421410111, PMID: 25453081

Zaidi M, Datta HK, Patchell A, Moonga B, MacIntyre I. 1989. " calcium-activated " intracellular calcium elevation: a novel mechanism of osteoclast regulation. *Biochemical and Biophysical Research Communications* **163**:1461–1465. DOI: https://doi.org/10.1016/0006-291x(89)91143-1, PMID: 2783143

Zaidi M, Shankar VS, Towhidul Alam AS, Moonga BS, Pazianas M, Huang CL. 1992. Evidence that a ryanodine receptor triggers signal transduction in the osteoclast. *Biochemical and Biophysical Research Communications* **188**:1332–1336. DOI: https://doi.org/10.1016/0006-291x(92)91377-3, PMID: 1445365

Zaidi M, Shankar VS, Tunwell R, Adebanjo OA, Mackrill J, Pazianas M, O'Connell D, Simon BJ, Rifkin BR, Venkitaraman AR. 1995. A ryanodine receptor-like molecule expressed in the osteoclast plasma membrane functions in extracellular Ca2+ sensing. *The Journal of Clinical Investigation* **96**:1582–1590. DOI: https://doi.org/10.1172/JCI118197, PMID: 7657829

Zaidi M. 2007. Skeletal remodeling in health and disease. *Nature Medicine* **13**:791–801. DOI: https://doi.org/10.1038/nm1593, PMID: 17618270

Zaidi M, Sun L, Robinson LJ, Tourkova IL, Liu L, Wang Y, Zhu LL, Liu X, Li J, Peng Y, Yang G, Shi X, Levine A, Iqbal J, Yaroslavskiy BB, Isales C, Blair HC. 2010. Acth protects against glucocorticoid-induced osteonecrosis of bone. *PNAS* **107**:8782–8787. DOI: https://doi.org/10.1073/pnas.0912176107, PMID: 20421485

Zaidi M, Iqbal J. 2012. Translational medicine: double protection for weakened bones. *Nature* **485**:47–48. DOI: https://doi.org/10.1038/485047a, PMID: 22552091

Zaidi M, Iqbal J. 2016. Closing the loop on the bone-resorbing osteoclast. *Nature Medicine* **22**:460–461. DOI: https://doi.org/10.1038/nm.4104, PMID: 27149217

Zanotti S, Smerdel-Ramoya A, Stadmeyer L, Durant D, Radtke F, Canalis E. 2008. Notch inhibits osteoblast differentiation and causes osteopenia. *Endocrinology* **149**:3890–3899. DOI: https://doi.org/10.1210/en.2008-0140, PMID: 18420737

Zelcer N, Tontonoz P. 2006. Liver X receptors as integrators of metabolic and inflammatory signaling. *The Journal of Clinical Investigation* **116**:607–614. DOI: https://doi.org/10.1172/JCI27883, PMID: 16511593

Zhang J, Niu C, Ye L, Huang H, He X, Tong W-G, Ross J, Haug J, Johnson T, Feng JQ, Harris S, Wiedemann LM, Mishina Y, Li L. 2003. Identification of the haematopoietic stem cell niche and control of the niche size. *Nature* **425**:836–841. DOI: https://doi.org/10.1038/nature02041, PMID: 14574412

Zhang R, Oyajobi BO, Harris SE, Chen D, Tsao C, Deng HW, Zhao M. 2013. Wnt/ B -Catenin signaling activates bone morphogenetic protein 2 expression in osteoblasts. *Bone* **52**:145–156. DOI: https://doi.org/10.1016/j.bone.2012.09.029, PMID: 23032104

Zhang J, Valverde P, Zhu X, Murray D, Wu Y, Yu L, Jiang H, Dard MM, Huang J, Xu Z, Tu Q, Chen J. 2017. Exercise-induced irisin in bone and systemic irisin administration reveal new regulatory mechanisms of bone metabolism. *Bone Research* **5**:16056. DOI: https://doi.org/10.1038/boneres.2016.56, PMID: 28944087

Zhao M, Qiao M, Harris SE, Oyajobi BO, Mundy GR, Chen D. 2004. Smurf1 inhibits osteoblast differentiation and bone formation in vitro and in vivo. *The Journal of Biological Chemistry* **279**:12854–12859. DOI: https://doi.org/10.1074/jbc.M313294200, PMID: 14701828

Zhao C, Irie N, Takada Y, Shimoda K, Miyamoto T, Nishiwaki T, Suda T, Matsuo K. 2006. Bidirectional ephrinb2-ephb4 signaling controls bone homeostasis. *Cell Metabolism* **4**:111–121. DOI: https://doi.org/10.1016/j.cmet.2006.05.012, PMID: 16890539

Zhao B, Takami M, Yamada A, Wang X, Koga T, Hu X, Tamura T, Ozato K, Choi Y, Ivashkiv LB, Takayanagi H, Kamijo R. 2009. Interferon regulatory factor-8 regulates bone metabolism by suppressing osteoclastogenesis. *Nature Medicine* **15**:1066–1071. DOI: https://doi.org/10.1038/nm.2007, PMID: 19718038

Zhou S, Turgeman G, Harris SE, Leitman DC, Komm BS, Bodine PVN, Gazit D. 2003. Estrogens activate bone morphogenetic protein-2 gene transcription in mouse mesenchymal stem cells. *Molecular Endocrinology* **17**:56–66. DOI: https://doi.org/10.1210/me.2002-0210, PMID: 12511606

Zhu H, Kavsak P, Abdollah S, Wrana JL, Thomsen GH. 1999. A Smad ubiquitin ligase targets the BMP pathway and affects embryonic pattern formation. *Nature* **400**:687–693. DOI: https://doi.org/10.1038/23293, PMID: 10458166

Zhu LL, Blair H, Cao J, Yuen T, Latif R, Guo L, Tourkova IL, Li J, Davies TF, Sun L, Bian Z, Rosen C, Zallone A, New MI, Zaidi M. 2012a. Blocking antibody to the β-subunit of FSH prevents bone loss by inhibiting bone resorption and stimulating bone synthesis. *PNAS* **109**:14574–14579. DOI: https://doi.org/10.1073/pnas.1212806109, PMID: 22908268

Zhu LL, Tourkova I, Yuen T, Robinson LJ, Bian Z, Zaidi M, Blair HC. 2012b. Blocking FSH action attenuates osteoclastogenesis. *Biochemical and Biophysical Research Communications* **422**:54–58. DOI: https://doi.org/10.1016/j.bbrc.2012.04.104, PMID: 22561017

Zhu J, Zhang C, Jia J, Wang H, Leng H, Xu Y, Wu C, Zhang Q, Song C. 2021. Osteogenic effects in a rat osteoporosis model and femur defect model by simvastatin microcrystals. *Annals of the New York Academy of Sciences* **1487**:31–42. DOI: https://doi.org/10.1111/nyas.14513, PMID: 33098131