



REVIEW

Open Access

From nerve to bone: a tale of autonomic nervous system, bone cells, and beyond

Wei-Jun Huang^{1,2†}, Yong-Kang Hu^{1,3†}, Heng-Zhen Li^{1,2}, Wen-Hao Lu^{1,2}, Guang Yang^{1,2}, Bing-Zhou Ji^{1,2}, Wen-Feng Xiao^{1,2*} and Yu-Sheng Li^{1,2*}

Abstract

Bone is a multifunctional organ essential for structural support, protection, hematopoiesis, and endocrine regulation. Emerging research increasingly highlights the pivotal role of the nervous system in bone metabolism, repair, and musculoskeletal disease progression, particularly the autonomic nervous system (ANS), which precisely regulates bone tissue cells via sympathetic and parasympathetic pathways. The ANS regulates the activity of mesenchymal stem cells (MSCs), osteoblasts, osteoclasts, chondrocytes, and nucleus pulposus cells (NPCs) via neurotransmitters such as norepinephrine (NE), acetylcholine (ACh), neuropeptide Y (NPY), and vasoactive intestinal peptide (VIP), thereby modulating core pathological processes in bone-related disorders including osteoporosis (OP), osteoarthritis (OA), intervertebral disc degeneration (IVDD), and traumatic fractures. Targeted neuromodulation is emerging as a promising therapeutic strategy for musculoskeletal disorders. This review aims to summarize the regulatory roles of the ANS in bone cell metabolism and bone-related pathologies and to evaluate current ANS-bone axis-based interventions to promote skeletal health and alleviate the burden of musculoskeletal diseases.

Key words Autonomic nervous system (ANS), Neurotransmitters, Bone tissue cells, Bone metabolism, Bone-related diseases, Therapeutic strategies

Background

Bone serves as a vital organ in mammals, providing not only structural support and protection for internal organs but also participating in key physiological processes such as hematopoiesis, mineral storage, and endocrine regulation [1,2]. To sustain these diverse functions, the nervous system plays an essential role in regulating bone metabolism, maintaining homeostasis, and promoting tissue repair [3]. Nerve fibers are extensively and intricately distributed in the skeleton, particularly in the periosteum, mineralized bone, and bone marrow. They not only mediate mechanical and pain sensation but also serve critical functions in maintaining skeletal integrity and facilitating bone repair [4-6]. In addition to regulating bone tissue cells, the nervous system is also deeply involved in the development and progression of various skeletal disorders, such as osteoporosis (OP) and osteoarthritis (OA) [7]. Therefore, the nervous system is essential for maintaining skeletal physiology.

The autonomic nervous system (ANS) consists of the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS), which often exhibit antagonistic physiological effects [8]. The SNS primarily mediates stress responses by releasing norepinephrine (NE), which promotes bone resorption and influences cellular metabolism within the joints [9]. In contrast, the PSNS mainly secretes acetylcholine (ACh) to regulate inflammation and repair processes in bone and joint tissues [10]. Meanwhile, enhanced parasympathetic activity can reduce the levels of inflammatory mediators in synovial fluid, thereby alleviating joint pain and swelling [11]. Furthermore, sympathetic nerve fiber-derived neurotransmitters such as vasoactive intestinal peptide (VIP) are pivotal in intervertebral disc degeneration (IVDD), mitigating inflammation and degeneration of disc cells via the fibroblast growth factor (FGF) 18/fibroblast growth factor receptor (FGFR) 2 signaling pathway [12]. Together, these findings highlight the essential role of the ANS in skeletal homeostasis, repair, and the pathogenesis as well as management of musculoskeletal diseases.

The ANS regulates not only bone homeostasis and repair at the systemic level, but also precisely modulates the differentiation of mesenchymal stem cells (MSCs) [13,14], the

[†]Wei-Jun Huang and Yong-Kang Hu contributed equally to this work

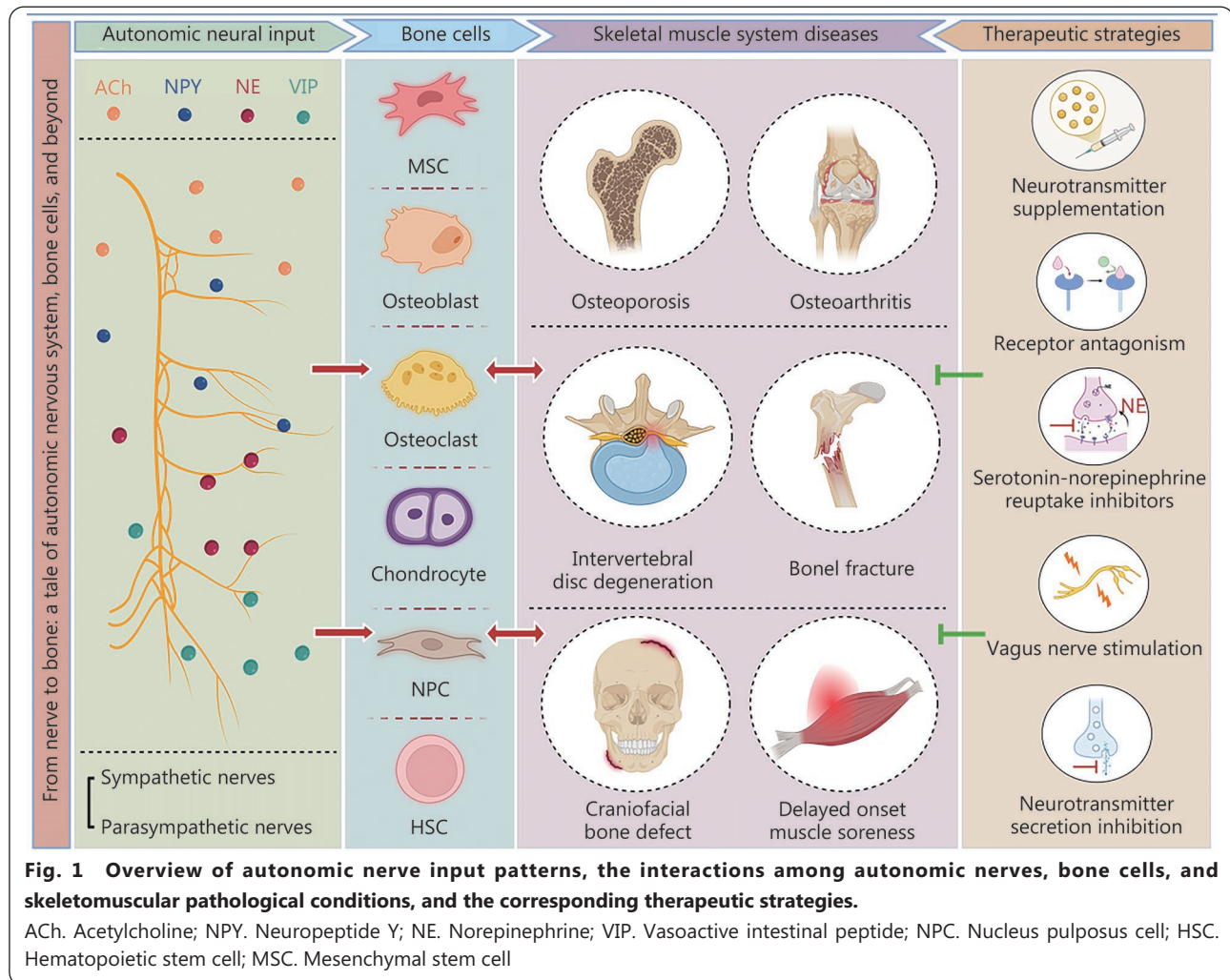
*Correspondence: Wen-Feng Xiao, xiaowenfeng@csu.edu.cn; Yu-Sheng Li, liyusheng@csu.edu.cn

¹Department of Orthopedics, Xiangya Hospital, Central South University, Changsha 410008, China

Full list of author information is available at the end of the article

activity of osteoblasts [15] and osteoclasts [16,17], the fate of chondrocytes [18] and nucleus pulposus cells (NPCs) [19,20], and the maintenance of hematopoietic stem cell (HSC) niches in the bone marrow [21], underscoring its multilayered regulatory capacity. For instance, the cholinergic activity of the PSNS promotes osteoblast proliferation and induces osteoclast

apoptosis, which supports bone repair and remodeling [22]. This review aims to systematically analyze the complex interactions between the ANS and the skeletal system, further elucidate the potential roles of the nervous system in bone metabolism and bone-related diseases, and explore its prospects as a therapeutic target in clinical applications (Fig. 1).



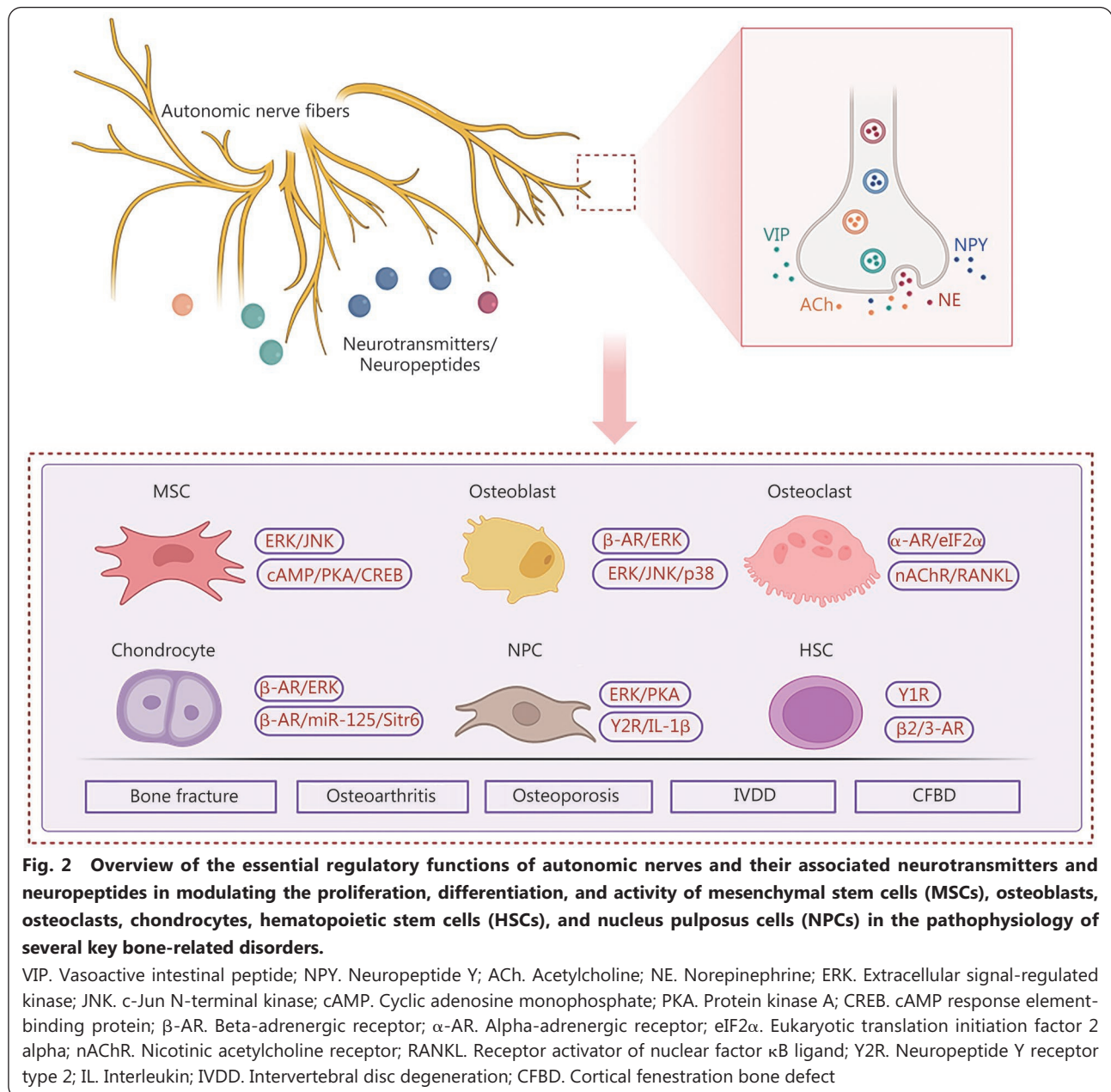
Autonomic nervous system in bone: neurotransmitters and receptors

The nervous system consists of the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system, which comprises the cranial and spinal nerves. The peripheral nervous system is further divided into the somatic nervous system and ANS, also referred to as the vegetative nervous system. The sympathetic and parasympathetic nerves of the ANS are extensively and intricately distributed throughout the cardiac muscle, smooth muscle, and glands [23,24]. Beyond classical neurotransmitters such as NE and ACh, bioactive factors including neuropeptide Y (NPY), VIP, dopamine (DA), and leptin, as well as their

corresponding receptors, specifically modulate ANS-mediated bone metabolism (Fig. 2). Evidence from animal studies demonstrated that autonomic nerve fibers innervate the periosteum during embryonic development and later extend into the metaphyseal and epiphyseal regions of long bones [5,25]. Specifically, sympathetic nerve fibers are particularly densely distributed in bone tissue, especially within the periosteum [5].

Sympathetic regulation via norepinephrine-adrenergic receptor signaling

NE is primarily synthesized and released by the sympathetic nerves, with a small amount secreted by chromaffin cells in



the adrenal medulla. It serves as the main neurotransmitter of sympathetic signaling [5]. The synaptic transmission of NE mainly comprises a series of well-organized steps, wherein NE is synthesized in neurons, packaged into vesicles, released into the synaptic cleft, reabsorbed by transporters, and ultimately degraded by enzymes [24]. The synthesis of NE begins with tyrosine, which is converted to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase. L-DOPA is then converted to DA by L-aromatic amino acid decarboxylase. DA is subsequently transported into synaptic vesicles by the vesicular monoamine transporter, where it is converted to NE by DA β -hydroxylase [26].

Adrenergic receptors (ARs) primarily mediate their

functions through binding to NE and epinephrine [27]. Molecular cloning has revealed that the family of alpha-adrenergic receptors (α -ARs) comprises two distinct subtypes, α 1-AR and α 2-AR, while the family of beta-adrenergic receptors (β -ARs) encompasses β 1-AR, β 2-AR, and β 3-AR subtypes. All AR subtypes are members of the G protein-coupled receptor (GPCR) superfamily [28].

Parasympathetic modulation via cholinergic signaling

ACh functions as the principal neurotransmitter of the PSNS, governing involuntary physiological processes including heart rate, gastrointestinal motility, smooth muscle tone, and exocrine gland secretion [8]. ACh-mediated neurotransmission

is orchestrated by a sequence of tightly integrated steps: ACh synthesis, vesicular packaging, storage within synaptic vesicles, exocytotic release into the synaptic cleft, reuptake via presynaptic transporters, and enzymatic degradation by acetylcholinesterase [24].

Cholinergic receptors are divided into two distinct categories according to their responsiveness to the specific agonists nicotine and muscarine: nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). Among them, nicotinic receptors include the neuronal type (N1), which is in the CNS and autonomic ganglia, and the muscle type (N2), which is found at neuromuscular junctions. Muscarinic receptors are chiefly localized in autonomic effector organs and comprise five subtypes (M1–M5), all of which function as GPCRs [29,30].

Roles of other neuropeptides, related neuromodulators, and their receptors

Neuropeptide Y

NPY is a highly conserved 36-amino acid peptide, predominantly found in the arcuate nucleus of the hypothalamus within the CNS. It can also be released by the adrenal medulla and the sympathetic nerves in response to chronic stress [31]. NPY receptors include five subtypes: Y1Rs, Y2Rs, Y4Rs, Y5Rs, and Y6Rs [32], all of which are GPCRs. They are highly expressed in various brain regions and the ANS. Among them, Y1Rs, Y2Rs, and Y6Rs are involved to some extent in the regulation of bone homeostasis [31,33,34]. Previous studies demonstrated the osteoprotective effects of Y2R ablation, revealing that global knockout increased trabecular bone formation [34–37], whereas hypothalamus-specific deletion prevented sex hormone deficiency-induced bone loss [38]. Collectively, Y2Rs function as critical negative regulators of bone mass, indicating that the targeted inhibition of central or peripheral Y2R signaling may offer a promising strategy to mitigate pathological bone loss induced by chronic stress.

Vasoactive intestinal peptide

VIP was originally discovered to be expressed in the small intestine and lungs. VIP is widely distributed throughout the SNS [39]. In the PSNS, VIP is typically co-released with ACh at parasympathetic nerve terminals [8]. The VIP released from these fibers plays a key role in regulating bone metabolism, bone remodeling, and maintaining bone homeostasis [40,41]. VIP mainly exerts biological effects through two GPCR-B: vasoactive intestinal peptide receptor (VPAC)1 and VPAC2 [42,43]. Furthermore, VPAC1 and VPAC2 are expressed on both osteoblasts and osteoclasts during cranial bone

differentiation [44,45]. Upon specific receptor engagement, VIP orchestrates the functional coupling of these bone cells, thereby preserving skeletal integrity.

Dopamine

DA is a neuropeptide widely distributed in the CNS and peripheral tissues. In the peripheral tissues, DA, as a precursor of NE and epinephrine, is abundantly stored in sympathetic nerves and can directly modulate skeletal cells to regulate bone metabolism [16]. A previous study showed that mice with DA transporter deficiency exhibit low bone mass, highlighting an essential contribution of the dopaminergic pathway in regulating bone remodeling [46]. DA deficiency or excess is linked to neuropsychiatric disorders such as Parkinson's disease and schizophrenia. Patients with these conditions often have a higher risk of osteoporotic fractures than healthy individuals, suggesting that DA levels may influence bone mass [47]. DA exerts its biological effects through five distinct GPCRs, namely D1–D5 [48–50]. These receptors are found in various cell types, such as bone marrow mesenchymal stem cells (BMSCs), osteoblasts, and osteoclasts, and participate extensively in modulating the skeletal microenvironment [16,51,52].

Leptin

Leptin is a cytokine-like peptide hormone secreted by adipose tissue, essential for the regulation of food intake and energy metabolism [53,54]. It has been identified that leptin receptors are expressed in peripheral tissues such as skeletal muscle and bone, as well as in various skeletal cell types [55,56]. However, the role of leptin in regulating bone homeostasis remains a subject of debate. To address this controversy, we propose a unifying “metabolism-dependent central-peripheral dual-regulation model”. Within this framework, the dominant regulatory mechanism shifts dynamically depending on central leptin sensitivity. Within this framework, when central leptin sensitivity is preserved under physiological conditions, regulatory control is predominantly exerted through central pathways. In this state, elevated central leptin levels amplify sympathetic tone, which suppresses osteoblast proliferation and stimulates osteoclast activity primarily via β 2-ARs, ultimately accelerating trabecular bone loss [57–60]. Conversely, the peripheral circuit acts as the primary mediator under metabolic disorders such as obesity and metabolic syndrome. Specifically, obesity-induced central leptin resistance attenuates central inhibitory signaling. Accordingly, circulating leptin directly activates long-form receptors (LepRb) on bone cells, eliciting cellular responses

that counteract central regulation. This local interaction promotes cortical bone apposition and increases total bone mass [55,56,61]. To validate this model, future studies should investigate osteoblast-specific *Lepr* knockout mice (such as *Osx-Cre; Lepr^{fl/fl}*) across different metabolic conditions. Comparing these mutants with wild-type controls under normal or high-fat dietary conditions effectively verifies the distinct peripheral and central mechanisms. Under obese conditions, wild-type mice are expected to exhibit peripheral leptin-driven bone formation, whereas the knockout models lack this response. This strategy would confirm that the peripheral circuit dominates the central axis only after central resistance develops.

Endocannabinoids

The endocannabinoid system (ECS) comprises endogenous cannabinoids, their receptors [cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2)], and a set of downstream enzymes [62,63]. Notably, CB1 is found at peripheral sympathetic nerve terminals associated with bone [64], with minimal expression on the surface of BMSCs, osteoblasts, osteoclasts, and osteocytes. In contrast, CB2 is highly expressed in osteoblasts, osteoclasts, and osteocytes [65,66]. The ECS can exert a critical influence on regulating bone remodeling and bone quality by modulating the SNS [62,67,68]. Researchers found that endogenous cannabinoid 2-arachidonoylglycerol (2-AG) produced by osteoblasts binds to presynaptic CB1 in sympathetic neurons, thereby inhibiting NE release. This reduced the NE-induced suppression of bone formation mediated by β 2-ARs on osteoblasts [65,67,69]. In summary, the ECS is essential for skeletal health.

Autonomic nervous system and neuropeptide-mediated regulation of bone tissue cells

Fate of mesenchymal stem cells

MSCs are multipotent progenitor cells derived from the mesoderm and characterized by a fibroblast-like morphology. They can differentiate into osteoblasts and chondrocytes, thereby contributing to skeletal homeostasis and participating in the pathogenesis of age-related diseases as well as in cell-based therapeutic strategies [70]. Bone marrow stromal MSCs have been extensively characterized and are regarded as a principal MSC source because of their abundance and relatively stable differentiation capacity [71]. With the growing interest in neuro-skeletal interactions, recent studies have increasingly highlighted the regulatory role of the ANS in determining MSC fate, particularly through sympathetic signaling [13,34,72]. Notably, the evidence suggests that the

SNS not only directly regulates BMSC differentiation but also modulates the bone marrow microenvironment to indirectly influence BMSC-HSC interactions [13].

The ANS finely modulates MSCs through various neurotransmitters and regulatory factors. Within sympathetic signaling networks, NE exerts divergent, context-dependent effects on MSC biology. For instance, high concentrations of NE (10^{-6} – 10^{-5} mol/L) markedly suppressed human BMSC proliferation by activating the β 2-AR-mediated extracellular signal-regulated kinase (ERK)1/2-protein kinase A (PKA) pathway [73]. However, this inhibitory effect occurred under sustained, supraphysiological NE exposure *in vitro*, potentially amplifying β 2-AR signaling beyond its physiological range. Thus, this robust response likely represents an exaggerated form of baseline β 2-AR regulation rather than a direct reflection of normal sympathetic tone. In contrast, under severe metabolic stress, particularly glucotoxicity, NE exerted a paradoxical cytoprotective effect on murine MSCs. Mechanistically, NE signaling activated the protein kinase B (Akt)/B-cell lymphoma 2 (Bcl-2) axis via α -ARs, downregulating Bcl-2-associated X protein (Bax) and cleaved caspase-3 while limiting reactive oxygen species (ROS) accumulation to attenuate apoptosis [74]. Crucially, this α -AR-mediated survival response emerges specifically under pathological stress, suggesting a microenvironment-dependent shift in receptor engagement. Collectively, these findings imply a physiological “receptor shift” in the sympathetic regulation of MSCs. Under basal conditions, β 2-AR signaling appears to exert a tonic restraint on osteogenesis, consistent with *in vivo* evidence from rabbit models where β 2-AR blockade significantly upregulated osteogenic markers [75]. Conversely, during metabolic or oxidative stress, α -AR pathways may dominate to promote cell survival as a compensatory adaptation. Nevertheless, extrapolating extreme *in vitro* paradigms directly to physiological bone remodeling warrants caution. Rigorous validation necessitates graded, physiologically relevant NE exposure models in genetically tractable mice, combined with MSC-lineage-specific adrenergic receptor beta 2 (*Adrb2*) deletion and subtype-selective α -AR modulation to delineate nerve-derived from cell-autonomous effects. Integrating this framework with lineage tracing and dynamic histomorphometry will ultimately determine whether a context-dependent shift in receptor dominance truly occurs *in vivo*.

In concert with the sympathetic axis, cholinergic signaling dictates MSC dynamics and lineage commitment. *Ex vivo* analyses of human trauma-derived MSCs revealed that AChR levels dynamically shift, exhibiting upregulation during

osteogenesis and downregulation during adipogenesis [76]. However, these *ex vivo* findings primarily establish correlative, rather than causal, relationships. For instance, MSCs derived from trauma tissues are exposed to severe inflammation, which can easily alter the basal receptor expression of the cells. Additionally, *in vitro* experiments in rat BMSCs indicated that native ACh promoted cell migration via the mAChR-mediated Ca^{2+} /protein kinase C (PKC)/ERK1/2 signaling pathway [77]. Moreover, treating human MSCs with the nAChR agonist nicotine elicited a biphasic response: low doses (10^{-7} mol/L) promoted Ca^{2+} influx and cell migration, whereas higher doses (10^{-5} mol/L) paradoxically induced apoptosis and impaired directed chemotaxis [78]. Unlike natural ACh, nicotine is poorly degraded by the enzyme, which prolongs cholinergic channel opening, leading to toxic calcium overload [78]. Consequently, this *in vitro* model may not fully represent the brief, natural cholinergic signaling that occurs *in vivo*.

In addition, ANS-mediated secretion of osteocyte-derived NPY suppressed BMSC osteogenesis while promoting adipogenesis, leading to a bone-fat metabolic imbalance. Notably, this negative regulation was reversed in an osteocyte-specific NPY^{fl/fl} mouse model [79]. Conversely, in a rat femoral fracture model, melatonin intervention accelerated fracture healing by upregulating NPY and Y1Rs, which significantly enhanced MSC proliferation and migration. This pro-osteogenic effect was blunted by the Y1R antagonist BIBP3226 [80]. Such divergent effects of NPY on BMSC fate determination are likely due to a distinct microenvironment. Within physiological homeostasis, osteocyte-derived NPY may act as a paracrine inhibitor to restrict basal bone formation. In contrast, during acute trauma such as fractures, NPY-signaling may be dynamically reprogrammed into a pro-regenerative stimulus, mobilizing rapid BMSC expansion and tissue repair.

In cultured human BMSCs, VIP upregulated early osteogenic markers and facilitated cytoskeletal remodeling required for bone matrix formation [34]. In a rat cranial defect model, VIP further enhanced bone regeneration and local angiogenesis. Mechanistically, these effects were associated with activation of the Wnt/ β -catenin pathway in BMSCs, leading to augmented osteogenic differentiation and increased vascular endothelial growth factor (VEGF) expression [80]. Moreover, in a murine model of 6-hydroxydopamine (6-OHDA)-induced sympathetic denervation, VIP administration effectively restored impaired fracture healing [40]. Collectively, these findings support a protective and pro-regenerative role for VIP in skeletal remodeling and repair. In contrast to the pro-regenerative effects of VIP, DA signaling exhibits conflicting results in rat BMSC *in vitro* models. One

study reported that DA promoted osteogenic differentiation through dopamine receptor D1 (D1R)-mediated ERK activation [81]. By contrast, another investigation showed that DA suppressed osteogenesis by inhibiting the Akt/glycogen synthase kinase (GSK)-3 β / β -catenin pathway [51]. This pronounced discrepancy may be associated with DA's non-selective receptor binding and the engagement of distinct DR subtypes that trigger divergent downstream signaling cascades (Table 1) [14,34,40,51,73-75,77,78,80-83].

Osteoblast differentiation

Osteoblasts are chiefly derived from BMSCs, with some eventually differentiating into osteocytes embedded in the bone matrix. These cells are critical for regulating the bone microenvironment [84,85]. In addition, osteoblasts largely promote the deposition of nascent extracellular matrix (ECM) through the secretion of extracellular proteins, such as type I collagen, osteocalcin (OCN), osteopontin (OPN), and alkaline phosphatase (ALP), thereby mediating bone formation [29,86]. Current studies emphasize the critical involvement of the ANS in the development and regulation of the function of osteoblasts [86-89]. For instance, in the bone microenvironment, adrenergic signaling from the SNS stimulates osteoblasts to secrete active factors such as interleukin (IL)-6, IL-1 β , IL-11, tumor necrosis factor (TNF), prostaglandin E2 (PGE2), and vascular endothelial growth factor A (VEGF-A) [90-92]. However, cholinergic signaling from the PSNS may directly drive the proliferation and differentiation of osteoblasts [93,94].

The molecular basis for this neuro-osteogenic communication lies in direct receptor engagement. Recent studies have confirmed that α -ARs, β -ARs, nAChRs, and mAChRs are expressed on the surface of osteoblasts [95-99]. Among these receptors, the β 2-ARs act as the principal transducers of systemic sympathetic signals. Downstream of the receptors, molecular clock genes were identified in period circadian regulator 1 and period circadian regulator 2 double-knockout (Per1/2^{-/-}) mouse models as essential mediators of leptin-driven suppression of bone formation. In osteoblasts, SNS- β 2-AR signaling simultaneously activated two mechanistically antagonistic pathways. Specifically, one pathway constituted a predominant inhibitory axis, in which cAMP response element-binding protein (CREB)-dependent upregulation of clock genes suppressed the cellular myelocytomatosis oncogene (*c-Myc*) and *cyclin D1*, thereby arresting cell-cycle progression. Conversely, a parallel pathway mediated by activator protein 1 (AP-1) promoted proliferation [96,100]. Mechanistically, the molecular clock

Table 1 Autonomic nerves and associated mediators exert diverse biological effects on MSCs through distinct signaling mechanisms.

Autonomic neurotransmitter and neuropeptide signaling	Receptors	Signaling pathways	Experimental model systems	Biological functions	References
SNS	β1-AR	MAPK-ERK1/2/JNK/p38	Normotensive (Wistar) and spontaneously hypertensive rats	Early osteogenic differentiation, expression of Runx2, osterix, and β-catenin↑	[14]
	β2-AR	NA	BMSCs of New Zealand rabbits	Osteogenic differentiation↓; Proliferation, migration↑	[75]
	nAChR	NA	Human BMSCs	Spontaneous migration↑	[78]
SNS/NE	β2-AR	MAPK-ERK1/2; cAMP-PKA	Human BMSCs	Proliferation in high NE density↓	[73]
	β3-AR	NA	Rats underwent TCST	SDF-1-induced migration↓; Osteogenic differentiation↓; Expression of ALP, OCN, and Runx2↓	[82]
	α-AR	Akt/Bcl-2	Diabetic mice underwent SYMX; Mouse BMSCs	Apoptosis induced by high glucose↓; ROS induced by high glucose↓	[74]
ACh	m1AChR	Ca ²⁺ -PKCζ-ERK1/2	Rat BMSCs	Migration induced by ACh in a time- and dose-dependent manner↑	[77]
NPY	Y1R	cAMP-PKA-CREB	Osteocyte-specific NPY knockout mice (Dmp1-iCre; NPY ^{fl/yf}); NPY ^{fl/yf} control mice; Osteoblast-specific Cre mice (Col1a1-CreERT2; NPY ^{fl/yf})	Adipogenic differentiation↓; Osteogenesis↓; Bone loss and marrow adiposity accumulation↑	[34]
	Y1R	NA	Rat BMSCs; Femoral fracture model in rats	Proliferation↑; Migration↑; Osteoblastic differentiation↑; Expression of ALP, COL1A1, OCN, and Runx2↑	[80]
	NA	NA	Chemical SYMX mouse model; Mouse femur transverse fracture model	<i>In vitro</i> osteogenic differentiation↑; Expression of OCN and OPN↑	[40]
SNS/VIP	VPAC1/2	Wnt-β-catenin-Runx2; cAMP signaling pathway	Rat BMSCs; Human BMSCs	Expression of OPN, OCN, and VEGF↑; Osteogenic differentiation↑	[83]
DA	NA	Akt-GSK-3β-β-catenin	Rat BMSCs	Osteogenic differentiation↓; Adipogenic differentiation↑	[51]
	DIR	cAMP-PKA-ERK1/2-Runx2	Human BMSCs	Low DA density (5 nmol/L): osteogenic differentiation↑; High DA density (≥5 nmol/L): osteogenic differentiation↓	[81]

↑ Upregulation; ↓ Downregulation. NA. Not applicable; SNS. Sympathetic nervous system; PSNS. Parasympathetic nervous system; NE. Norepinephrine; ACh. Acetylcholine; NPY. Neuropeptide Y; VIP. Vasoactive intestinal peptide; DA. Dopamine; AR. Adrenergic receptor; nAChR. Nicotinic acetylcholine receptor; m1AChR. Muscarinic acetylcholine receptor m1; Y1R. Neuropeptide Y receptor type 1; VPAC. Vasoactive intestinal peptide receptor; DIR. Dopamine receptor D1; MAPK. Mitogen-activated protein kinase; ERK. Extracellular signal-regulated kinase; JNK. c-Jun N-terminal kinase; p38. p38 mitogen-activated protein kinase; cAMP. Cyclic adenosine monophosphate; PKA. Protein kinase A; Akt. Protein kinase B; Bcl-2. B-cell lymphoma 2; PKCζ. Protein kinase C zeta; CREB. cAMP response element-binding protein; Wnt. Wingless-related integration site; Runx. Runt-related transcription factor; GSK. Glycogen synthase kinase; BMSCs. Bone marrow mesenchymal stem cells; TCST. Transcutaneous electrical spinal cord stimulation; SYMX. Sympathectomy; SDF. Stromal cell-derived factor; ALP. Alkaline phosphatase; OCN. Osteocalcin; ROS. Reactive oxygen species; VEGF. Vascular endothelial growth factor; COL1A1. Collagen type I alpha 1 chain

functioned upstream of the AP-1 pathway, exerting a sustained repressive effect on AP-1 expression. Indeed, in *Per1/2*-deficient mice, the loss of *Per1/2* repression augmented AP-1-driven proliferation, resulting in a high-bone-mass phenotype. Consequently, under normal physiological conditions, clock-mediated suppression overrode anabolic signaling, leading to net bone loss within the leptin-sympathetic axis [96,100]. Upstream of this clock mechanism, the loss of $\beta 2$ -ARs in *Adrb2osb*^{-/-} mice similarly resulted in a high-bone-mass phenotype. Furthermore, although intracerebroventricular leptin infusion suppressed bone formation in wild-type mice, this anti-osteogenic effect was completely abolished in *Adrb2*-knockout animals [96,100]. Collectively, these findings confirm that central leptin-driven sympathetic signaling relies on osteoblastic $\beta 2$ -ARs to restrain bone accrual. Therefore, we propose that central leptin restrains bone formation via a sequential SNS-NE- $\beta 2$ -AR-clock gene axis in osteoblasts. This model can be directly tested by subjecting osteoblast-specific $\beta 2$ -ARs or *Per1/2* knockout mice to intracerebroventricular leptin infusion to determine whether disruption of this axis abolishes leptin-induced suppression of bone formation.

In contrast, increasing evidence highlights α -AR signaling as a potent stimulator of osteogenesis, contrasting with the canonical inhibitory role of $\beta 2$ -ARs. In human SaM-1 osteoblasts, NE binding to $\alpha 1B$ -ARs triggered dual mitogenic cascades, a Gq-coupled phosphoinositide-specific phospholipase C (PI-PLC)/Ca²⁺ axis and a Gi/o-Gbg-mediated suppression of K⁺ channels, which synergistically promoted osteoblast proliferation [101]. These anabolic effects were further corroborated by *in vivo* murine models, demonstrating that $\alpha 1B$ -AR activation upregulated the transcription factor CCAAT/enhancer-binding protein delta (EBP δ) to directly facilitate osteoblast expansion and bone accrual [97]. Furthermore, beyond these post-synaptic pro-osteogenic effects, pre-synaptic $\alpha 2$ -ARs also critically regulate skeletal homeostasis. For instance, the dual disruption of $\alpha 2A$ - and $\alpha 2C$ -ARs in mice led to excessive NE release and a paradoxically high bone mass phenotype [95]. This anomaly is primarily driven by compensatory hyperinsulinemia, which ultimately overrides direct catecholaminergic inhibition. Taken together, these findings reveal that SNS- α -AR signaling exerts a profound anabolic influence on osteoblasts.

Moreover, the mAChRs (M1–M5) were widely expressed in human primary osteoblasts and bone tissue, where they drove osteoblast proliferation via amplifying intracellular calcium signaling [102]. Conversely, *in vitro* murine MC3T3-E1 models revealed paradoxical nicotinic effects. Specifically, exogenous nicotine stimulated cyclin D1-

driven proliferation yet arrested p53-mediated osteogenic differentiation and mineralization. This process stalled osteoblasts at an immature stage, ultimately resulting in bone loss [102,103]. These conflicting cholinergic effects highlight a critical limitation of current neuroskeletal models. Importantly, this arrest in differentiation likely reflects pathological nicotinic receptor overactivation, similar to smoking-induced bone loss, rather than the physiological role of endogenous ACh, which relies on the coordinated action of both receptor types.

In a stress model using *NPY/Y2R* knockout mice, sympathetic signaling via NPY-Y2R suppressed NE release, which reduced the stress-induced inhibition of osteoblast activity and partially prevented stress-related bone loss [104]. This work is the first to demonstrate the protective role of NPY in stress-induced bone loss, suggesting a potential strategy for treating stress-related OP, including depression-associated bone loss. Other studies have shown that VIP binds to VPAC2 receptors on osteoblasts, activating G protein-coupled signaling, increasing intracellular cyclic adenosine monophosphate (cAMP), triggering the PKA pathway, increasing ALP activity, promoting bone matrix mineralization, and ultimately supporting osteogenesis [44,102,105]. Furthermore, the activation of D1R on MC3T3-E1 osteoblasts *in vitro* increased ERK1/2 phosphorylation and reversed dexamethasone-induced suppression of osteogenesis, whereas *in vivo* activation of D1Rs alleviated glucocorticoid-induced bone loss in rats [106]. These findings suggest that D1R may be a potential target for glucocorticoid-induced OP, although interventions directly targeting DA as a neurotransmitter have not been investigated. Overall, the current evidence indicates that NPY, VIP, and DA can promote osteoblast proliferation and differentiation, suggesting potential neural-based strategies to increase bone formation and mitigate bone loss.

Osteoclast activity

Osteoclasts originate from HSC-derived myeloid mononuclear precursors and participate in bone remodeling primarily by driving bone resorption [107]. Recently, the regulatory role of the ANS in osteoclastogenesis has garnered significant attention [5,108–110]. Within the bone microenvironment, osteoclast maturation and activation fundamentally depend on key local factors, such as receptor activator of nuclear factor κB ligand (RANKL), osteoprotegerin (OPG), macrophage colony-stimulating factor (M-CSF), IL-6, and so on [111–113]. Crucially, rather than being synthesized directly by nerve terminals, the expression of these factors is profoundly modulated by sympathetic efferent signals. Multiple studies have demonstrated that osteoclast maturation is primarily

driven by osteoblast- and chondrocyte-derived RANKL under the control of the SNS-NE- β 2-AR signaling pathway [107,114]. Specifically, the leptin-SNS-NE- β 2-AR axis was shown to activate the PKA-activating transcription factor 4 (ATF4) pathway in osteoblasts, leading to increased RANKL expression, which subsequently facilitated intercellular cross-talk to promote osteoclast precursor differentiation [115,116]. Supporting this indirect regulatory mechanism, low-dose propranolol (0.1 mg/kg) not only alleviated local inflammation by downregulating IL-1 β and TNF- α but also decreased RANKL and elevated OPG levels, thereby downregulating osteoclast-related genes [tartrate-resistant acid phosphatase (TRAP), cathepsin K, and matrix metalloproteinase (MMP)-9] via the nuclear factor of activated T cells cytoplasmic 1 (NFATc1) pathway [108]. This finding highlights the dual anti-inflammatory and anti-osteoclastogenic efficacy of β -blockers in OP therapy.

Beyond indirect regulation via osteoblast-derived RANKL, accumulating evidence suggests that the SNS exerts direct effects on osteoclasts [109,110]. *In vitro* studies have revealed that mature osteoclasts and their precursors express specific autonomic receptors, predominantly the β 2-AR subtype [109,110]. Direct stimulation with isoproterenol (ISO) increased intracellular ROS levels, subsequently upregulating NFATc1 and other osteoclast-related genes to promote osteoclastogenesis [110]. Furthermore, in stress models utilizing β 2-AR- or *miR-21*-knockout mice, sympathetic stress directly increased osteoclastic *miR-21* expression via β 2-AR signaling, which inhibited programmed cell death protein 4 (*Pdcd4*) and resulted in pronounced bone loss [109]. Conversely, the activation of endogenously expressed α 2-ARs on the osteoclast surface acted as a brake, suppressing RANKL-induced NFATc1, TRAP, and cathepsin K expression to curtail osteoclastogenesis [114].

Based on these findings, we hypothesize a concentration-dependent, dual-receptor gating model. Under conditions of chronic stress or inflammation characterized by elevated NE levels, low-affinity β 2-ARs become the dominant functional receptors. Their activation drives bone resorption through a two-pronged mechanism that indirectly upregulates the osteoblastic PKA-ATF4-RANKL axis and directly enhances osteoclastic ROS/*miR-21* signaling. In contrast, under physiological or low-NE conditions, catabolic β 2-AR signaling remains relatively quiescent. During these basal states, high-affinity α 2-ARs on osteoclasts act alongside presynaptic negative feedback to restrain excessive bone resorption.

In contrast to the primarily catabolic effects of the SNS, parasympathetic cholinergic signaling was demonstrated to

rely on ACh to counteract bone resorption by directly inducing osteoclast apoptosis [99,117]. This protective mechanism is mediated by specific cholinergic receptors expressed on the osteoclast surface. For instance, activation of nAChRs inhibited RANKL-induced calcium oscillations, triggering osteoclast apoptosis *in vivo* [117]. Similarly, muscarinic signaling was found to transduce parallel protective effects. Specifically, the M3 muscarinic acetylcholine receptors (M3Rs) acted as a pivotal downstream target for PSNS-derived ACh. Corroborating the functional importance of this ACh-M3R axis, M3R-deficient mice exhibited increased bone resorption parameters, including an enlarged osteoclast surface area [98]. These observations indicate that baseline cholinergic tone exerts a crucial restraining influence on osteoclastogenesis. Ultimately, the SNS and PSNS orchestrate osteoclast differentiation and activity through a delicate balance of antagonistic interactions to maintain dynamic skeletal homeostasis.

Moreover, another neuropeptide, VIP, can bind to pituitary adenylate cyclase-activating polypeptide type I receptor (PAC1) receptors to suppress osteoclast recruitment, a process associated with the upregulation of OPG and the down-regulation of RANKL and RANK expression [118,119]. Furthermore, studies in both animal and human cell models revealed that VIP not only inhibited osteoclast differentiation via the ERK and nuclear factor κ B (NF- κ B) signaling pathways, but also negatively modulated NFATc1, hence exerting anti-osteoclastogenic effects [45,119]. Specifically, DA could inhibit the maturation and activation of osteoclasts by suppressing the RANKL signaling pathway and reducing their bone-resorptive activity [120,121]. DA binding to dopamine receptor D2 (D2R) reduced intracellular cAMP levels and suppressed RANKL-induced cellular proto-oncogene *fos* (*c-Fos*) and *NFATc1* mRNA expression in human osteoclast precursors, thereby inhibiting osteoclastogenesis [122]. Additionally, DA was shown to inhibit osteoclast differentiation via the D2R/cAMP/PKA/CREB signaling pathway [16].

Unlike the NE- β 2-AR axis, which promotes osteoclast formation and activity, sympathetic signals mediated by VIP and DA tend to be inhibitory, indicating that osteoclast function is finely tuned by multiple sympathetic inputs to maintain bone homeostasis (Table 2) [45,75,96,98,100,106,108,109,114,115,117,123-125].

Chondrocytes homeostasis and differentiation

Chondrocytes, which originate from MSCs, are indispensable for preserving the structure and function of cartilage [126,127]. Under physiological conditions, mature chondrocytes

Table 2 Autonomic nerves and related mediators mediate complex cellular responses in osteoblasts and osteoclasts via specific signaling pathways

Autonomic neurotransmitter and neuropeptide signaling	Receptors	Signaling pathways	Experimental model systems	Biological functions	References
Osteoblasts					
SNS	β2-AR	CREB-c-Myc	Adrb2 ^{osb-/-} , Creb ^{osb-/-} , Atf4 ^{osb-/-} , and c-Myc ^{osb-/-} mice	Proliferation↓; Expression of cyclin D1/D2/E1, c-Myc, and Per1↓	[96]
SNS/NE	β2-AR	NA	Osteoblasts of New Zealand rabbits	Proliferation↑; Migration↑	[75]
Leptin (CNS)/SNS/NE	β2-AR	CREB-Per1/2/Cry1/2-c-Myc-cyclin D1; AP-1-c-Myc-cyclin D1	Per1/2- and Cry1/2-deficient mice	Osteoblast proliferation in the 1st pathway↓; Osteoblast proliferation in the 2nd pathway↑	[100]
PSNS	α1-AR	Cebpd-Ccne1	α1B ^{-/-} mice	Proliferation↑	[97]
	M3R	NA	M ₁ R ^{-/-} , M ₂ R ^{-/-} , M ₃ R ^{-/-} , M ₄ R ^{-/-} , M ₃ R ^{fl/fl} , α1(I)collagen-Cre and Adrb2 ^{-/-} mice	Bone mass accumulation↑; Proliferation↑	[98]
SNS/NPY	Y1R	cAMP signaling pathway	Col2.3GFPemd or Col2.3CFPC-yan mice	Differentiation↓; Mineralization↓	[125]
DA	D1R	MAPK-ERK1/2	Mouse BMSCs and MC3T3-E1 cells, overexpression and silencing of D1R in MC3T3-E1 cells, D1R-inhibited mice	Osteogenic differentiation↑; Expression of ALP, Runx2, and OSX↑; Glucocorticoid-induced bone loss↓	[106]
Osteoclasts					
SNS	β2-AR	NA	Murine osteoblasts/osteoclasts; Mice with bone loss	Osteoclast formation↑	[109,124]
	β2-AR	NFATc1 signaling pathway	Rats with administered propranolol; RAW264.7 osteoclast precursor cells	Osteoclastogenesis <i>in vitro</i> ↓; Expression of TRAP, cathepsin K, and MMP-9↓	[108]
	α2-AR	cAMP-NFATc1; eIF2α signaling pathway	RAW264.7 osteoclast precursor cells; Mouse primary bone marrow cells; Mouse mature osteoclasts	Osteoclastogenesis↓; Expression of TRAP, cathepsin K↓	[114]
Leptin (CNS)/SNS/NE	β2-AR	ATF4-RANKL; CART pathway	Adrb2 ^{osb-/-} , Creb ^{osb-/-} , Atf4 ^{osb-/-} , c-Myc ^{osb-/-} mice, Adrb2-deficient mice, ob/ob mice	Differentiation in the 1st signaling pathway, bone resorption in the 1st signaling pathway↑; Bone resorption in the 2nd signaling pathway↓	[115]
PSNS/ACh	nAChRs	RANK-Ca ²⁺ -NFATc1/c-Fos	nAChR subunit ^{-/-} mice; Bone marrow-derived macrophages	Osteoclastogenesis in high nAChR agonist density↓; Osteoclastogenesis in low nAChR agonist density↑	[117]
NPY	Y1R	Gi protein/cAMP/RANKL	Mouse osteoclast-like cells	Isoprenaline-induced osteoclastogenesis↓	[123]
VIP	VPAC1/2	NFATc1 signaling pathway	Human peripheral blood mononuclear cells	Differentiation, fusion, bone resorption↓; Expression of DCSTAMP, CTSK, MMP-9, TRAP, and ITGB3↓	[45]

↑ Upregulation; ↓ Downregulation. NA. Not applicable; SNS. Sympathetic nervous system; CNS. Central nervous system; NE. Norepinephrine; PSNS. Parasympathetic nervous system; NPY. Neuropeptide Y; DA. Dopamine; ACh. Acetylcholine; VIP. Vasoactive intestinal peptide; AR. Adrenergic receptor; mAChR. Muscarinic acetylcholine receptor; Y1R. Neuropeptide Y receptor type 1; D1R. Dopamine receptor D1; nAChRs. Nicotinic acetylcholine receptors; VPAC. Vasoactive intestinal peptide receptor; CREB. cAMP response element-binding protein; c-Myc. Cellular myelocytomatosis oncogene; AP-1. Activator protein 1; cAMP. Cyclic adenosine monophosphate; MAPK. Mitogen-activated protein kinase; ERK. Extracellular signal-regulated kinase; Nuclear factor of activated T cells cytoplasmic 1; RANK. Receptor activator of nuclear factor kappa-B; ATF4. Activating transcription factor 4; CART. Cocaine- and amphetamine-regulated transcript; Cry1. Cryptochrome 1; BMSCs. Bone marrow mesenchymal stem cells; MC3T3-E1. MC3T3-E1 cells; RAW. Ralph, Abelson, and Watson; ALP. Alkaline phosphatase; OSX. Osterix; TRAP. Tartrate-resistant acid phosphatase; MMP-9. Matrix metalloproteinase 9; DCSTAMP. Dendritic cell-specific transmembrane protein; CTSK. Cathepsin K; ITGB3. Integrin subunit beta 3; Cebpd. CCAAT/enhancer-binding protein δ; eIF2α. Eukaryotic translation initiation factor 2 alpha

maintain cartilage homeostasis by synthesizing and remodeling ECM components [128,129].

Recent studies have demonstrated extensive SNS innervation across cartilage, subchondral bone, and synovial tissues [130,131]. Consistent with this distribution, functional ARs are expressed on human articular chondrocytes, subchondral bone cells, and synovial fibroblasts [18,131-134]. Mechanistically, sympathetic signaling profoundly impairs chondrogenesis and joint homeostasis, a process well documented across multiple models. Providing the most direct clinical relevance, human MSCs and patient-derived chondrocyte progenitor cells exhibited sustained β 2-AR expression during chondrogenesis. Following local NE-mediated β 2-AR engagement, SRY-related HMG-box transcription factor 9 (SOX9) expression was downregulated, suppressing cartilage-specific matrix synthesis [type II collagen and sulfated glycosaminoglycans (sGAGs)] and upregulating hypertrophic markers (type X collagen and MMP-13), thereby impeding cartilage formation and driving hypertrophic differentiation [135]. Complementing these human cellular phenotypes, murine *in vivo* and primary cell models have further elucidated the underlying intracellular signaling cascades. In primary murine rib growth plate chondrocytes, β -AR agonist ISO stimulation activated PKA and ERK1/2 signaling, induced Jun-B expression, and suppressed SOX6 transcription, leading to decreased type II collagen levels [135]. However, this study reflects mainly developmental chondrogenesis and is less informative for adult cartilage degeneration or OA pathology. In naturally aged OA mouse models, the local NE- β 1-AR axis disrupted subchondral bone homeostasis by suppressing Sirtuin 6 (Sirt6) and promoting miR-125 upregulation in chondrocytes [136]. Furthermore, the specific mechanisms underlying systemic sympathetic influence have been elucidated using established cell lines. *In vitro* experiments utilizing the ATDC5 cell line demonstrated that epinephrine binding to chondrocytic β 2-ARs activated the cAMP/PKA pathway, resulting in reduced SOX9/5/6-dependent expression of matrix genes and impaired chondrogenesis [137]. Although epinephrine is not directly released from local sympathetic terminals, preganglionic sympathetic activation allows ACh to stimulate adrenal medullary chromaffin cells, thereby inducing systemic epinephrine secretion to indirectly govern chondrocyte function. Collectively, these converging findings establish the sympathetic-skeletal axis as a pivotal catabolic driver of cartilage degeneration. Operating through both local neural networks and systemic endocrine signals, aberrant adrenergic activation profoundly disrupts chondrocyte homeostasis.

In a destabilization of the medial meniscus-induced OA mouse model, NPY activated mechanistic target of rapamycin complex 1 (mTORC1) through neuropeptide Y receptor Y2 (NPY2R), which triggered Sma and Mad-related protein (SMAD)1/5/8 phosphorylation and subsequently aggravated cartilage degeneration and chondrocyte hypertrophy [31]. These observations indicate that the selective blockade of NPY2R may be a feasible therapeutic strategy for OA. Moreover, in terminally hypertrophic chondrocytes in mice, the binding of leptin to its receptor inhibited premature matrix mineralization, preserved the ordered arrangement of collagen fibrils, stabilized type X collagen expression, modulated terminal differentiation, and attenuated the excessive apoptosis of hypertrophic chondrocytes through multiple regulatory pathways [138,139]. Additionally, leptin treatment increased insulin-like growth factor 1 receptor expression in growth plates and mandibular condylar cartilage, thereby facilitating skeletal growth [140]. Collectively, the current evidence suggests that NPY and leptin are involved in maintaining cartilage homeostasis by modulating chondrocyte proliferation, hypertrophy, and matrix metabolism.

Nucleus pulposus cell metabolism

NPCs originate from the embryonic notochord and mainly consist of notochordal- and chondrocyte-like populations, forming the principal cellular components of the nucleus pulposus [141]. In the mature disc, NPCs are embedded in a matrix-rich environment and display round, oval, or polygonal morphologies. Due to their resemblance to chondrocytes, they are often termed chondrocyte-like cells [20]. Functionally, NPCs maintain ECM homeostasis and contribute to the immune and internal microenvironment of the intervertebral disc [142-144]. Disruption of their metabolic activity or cellular function contributes to the initiation and progression of IVDD [19].

NPCs are modulated by sympathetic neurotransmitters and their receptors, including NE and NPY [145,146]. Furthermore, in cultured human intervertebral disc cells, transcripts for almost all AR subtypes were detected, except for α 1D-AR and β 3-AR [147]. NE was reported to promote matrix catabolism in annulus fibrosus cells *in vitro* through activation of the ERK1/2 and PKA pathways, although the specific AR subtypes involved remain undefined [147]. In addition to NE, NPY affects NPC biology, but its precise molecular mechanisms were not fully elucidated. Further evidence indicated that NPY suppressed mitochondria-dependent apoptotic signaling, promoted NPC proliferation, protected cells from IL-1 β -induced apoptosis, and decreased

the expression of catabolic proteases, thereby potentially attenuating IL-1 β -induced matrix degradation [20]. These observations suggest that targeting NPY may delay the progression of IVDD by preserving NPC viability. Taken together, the current evidence supports the hypothesis that ANS signaling is actively involved in modulating NPC behavior during disc degeneration.

Hematopoietic stem cells, adipocytes, and tendon cells

HSCs reside in specialized bone marrow niches, maintaining their capacity for self-renewal and multilineage differentiation. Recent studies have identified bone marrow hematopoietic stem cells (BMHSCs) as key contributors to fracture healing [79,148,149]. Within this microenvironment, their migration, self-renewal, and differentiation are tightly governed by sympathetic innervation. Specifically, β 3-AR-mediated sympathetic signaling increased HSC proliferation and promoted their differentiation into emergency myeloid cells, thereby supporting fracture repair [148]. Conversely, the disruption of this adrenergic pathway not only reduced sympathetic nerve-driven inflammatory myeloid skewing [150,151] but also accelerated HSC aging, compromising overall hematopoietic function [152]. Alongside these adrenergic mechanisms, chronic stress elevated NPY levels within the bone marrow. Upon binding to osteoblastic Y1Rs, NPY modulated MMP-9 secretion, reducing the expression of hematopoietic stem and progenitor cell (HSPC) maintenance factors such as stromal cell-derived factor (SDF)-1 α , Kit ligand (Kitl), Angiopoietin 1 (Angpt1), and Vascular cell adhesion molecule 1 (Vcam1), and promoting HSPC mobilization into the peripheral circulation. Consequently, this mobilization decreased osteoclast numbers and alleviated ovariectomy-induced bone loss in mice [153]. However, as this study did not assess whether NPY directly alters intrinsic HSPC properties, such as cell cycle progression or cellular senescence, the contribution of HSPC-autonomous regulation to this mobilization process cannot be entirely ruled out.

Bone marrow adipose tissue (BMAT) within the skeleton and marrow cavity is a major cellular component of the bone marrow niche and skeletal microenvironment [113,154]. Previous studies have indicated that a subset of BMAT is modulated by the ANS, and that bone marrow adipocytes express large amounts of β -ARs [155,156]. Upon NE stimulation, these receptors activate the cAMP-PKA pathway, trigger lipolysis, and promote the release of free fatty acids and glycerol, thereby supporting the metabolic demands of cells in the bone marrow microenvironment [157-159]. Moreover, VIP was reported to induce lipolysis in primary rat and human

adipose tissues *in vitro* [160-162].

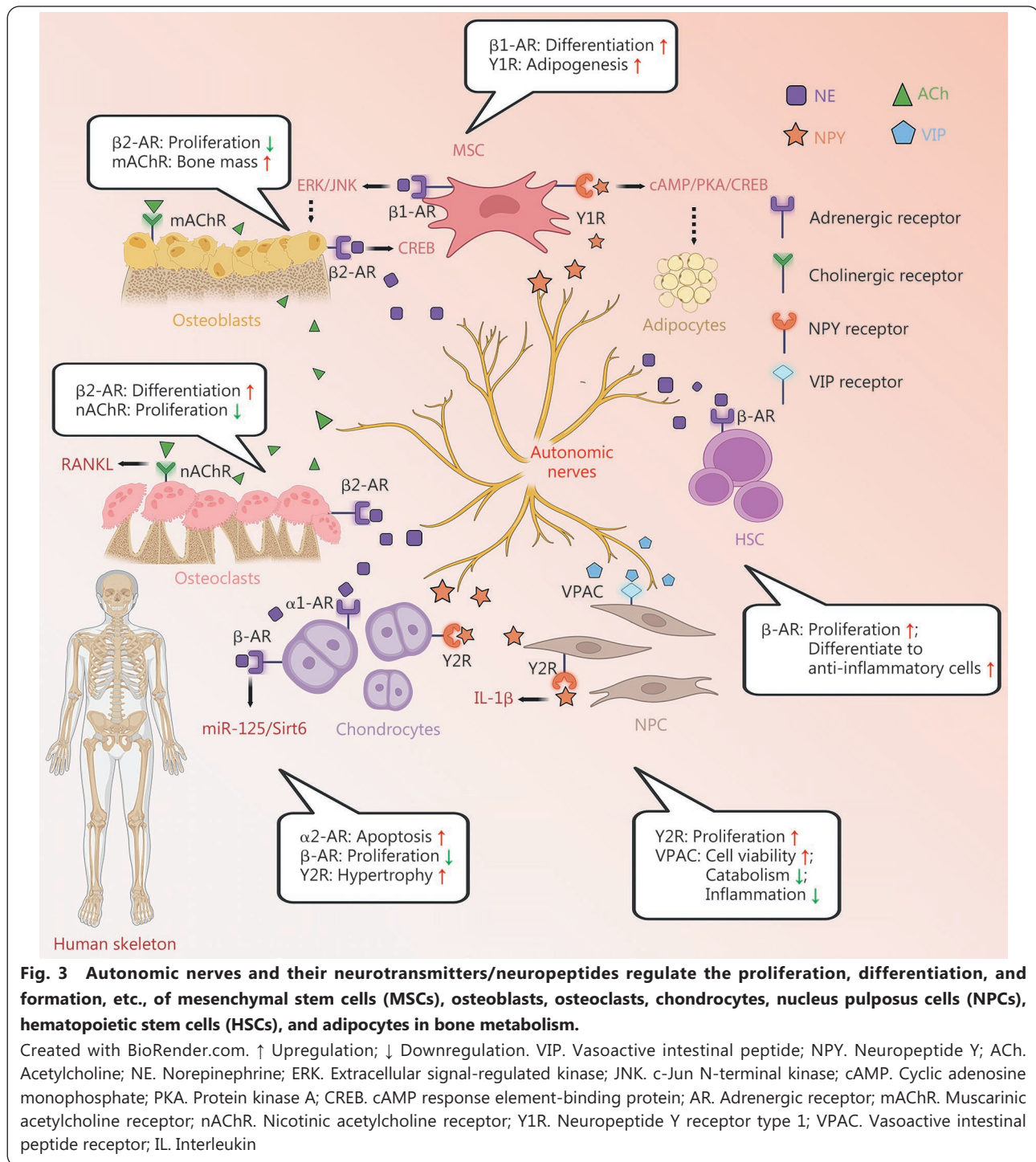
In addition to BMAT, tendon tissue also receives ANS innervation. During tendon injury and repair, multiple types of nerve fibers, including autonomic fibers, extend into the tendon proper and contribute to tissue regeneration [163-165]. The SNS regulates tendon function partly through the modulation of local blood flow, whereas the PSNS influences inflammatory responses in tendon tissue [164]. Furthermore, ACh was shown to increase tendon cell proliferation [166]. In summary, previous studies on ANS regulation of BMAT and tendon tissue have been limited and largely focused on the local effects of individual neurotransmitters or receptor subtypes. At present, a systematic understanding of the regulatory mechanisms in these two tissues is lacking. Moreover, the coordinated neural circuits involved in maintaining tissue homeostasis and supporting repair and regeneration remain insufficiently defined and warrant further investigation (Fig. 3, Table 3) [18,20,31,131,135,136,147,148,153,167].

The role of the autonomic nervous system and clinical implications in bone diseases

Osteoporosis

OP is a systemic skeletal disease characterized by a decrease in bone density, which leads to an increased susceptibility to fractures from minor falls, particularly in weight-bearing areas such as the spine and hip [168]. This condition predominantly affects the elderly and postmenopausal women. The resulting economic burden and consumption of social resources have made OP a major global public health concern [105]. Epidemiological data indicate that approximately 200 million individuals worldwide are affected by this disease [169]. The onset and progression of OP are regulated by osteoclast-mediated bone resorption and osteoblast-mediated bone formation [170]. Its treatment involves mainly pharmacological interventions, including antiresorptive medications (such as bisphosphonates and denosumab) and bone-forming agents (such as teriparatide) [171]. Although these treatments are effective, they are associated with certain adverse effects such as thromboembolic events, an increased stroke risk, and hypocalcemia, highlighting the urgent need for the development of safer and more effective therapeutic strategies [172].

The ANS plays a key role in regulating skeletal growth and bone metabolism, particularly in OP development [173]. Numerous studies have demonstrated that the SNS and its primary neurotransmitter, NE, regulate bone homeostasis through β -ARs [96,97,109]. Typically, this regulatory mechanism promotes osteoclast formation and inhibits



osteoblast function, resulting in increased bone resorption and decreased bone mass [174]. Furthermore, animal studies revealed that NE signaling suppressed parathyroid hormone (PTH)-induced osteoblast differentiation and mineralization, while promoting RANKL expression and osteoclast differentiation [88,131]. However, the β -blocker propranolol can partially counteract these effects and enhance PTH-induced osteogenesis [88]. In contrast, the NE- β 2-

AR signaling pathway has been shown to promote osteoblast proliferation and bone formation by upregulating AP-1 and cyclin D1 expression *in vitro* [100], which contradicts the widely accepted view that the SNS inhibits osteogenesis. These apparently contradictory findings likely reflect context-dependent differences in β 2-AR signaling. Under *in vitro* or acute stimulation conditions, transient β 2-AR activation promotes osteoblast proliferation via AP-1 and

Table 3 Autonomic nerves and related mediators orchestrate complex biological effects in chondrocytes, NPCs, and HSCs through distinct signaling mechanisms.

Autonomic neurotransmitter and neuropeptide signaling		Receptors	Signaling pathways	Experimental model systems	Biological functions	References
Chondrocytes						
SNS/NE	β2-AR	NA		Peripheral sympathectomy, OA-induced mice	OA-specific cartilage calcification↑	[131]
	β2-AR	AP-1 (Jun-B)		Growth plate chondrocytes prepared from ribs of embryonic E18.5 mice	Expression of type II collagen↓; Cartilage matrix synthesis↓	[135]
	α1-AR and β-AR	NA		Human OA cartilage chondrocytes	Expression of IL-8, MMP-13, GAG, type II collagen in high NE density (10 ⁻⁶ mol/L), proliferation in high NE density↓; Proliferation and apoptosis in low NE density (10 ⁻⁸ mol/L)↑	[18]
SNS/NPY	β1-AR	Sirt6/miR-125		Mouse natural aging model, a medial, and a load-induced meniscus instability model	Cartilage matrix degradation, cartilage damage↑	[136]
	Y2R	mTORC1-SMAD1/5/8-Runx2		Mouse OA model	Chondrocyte hypertrophy, matrix degradation↑; Chondrocyte autophagy↓; Chondrocyte apoptosis↑	[31]
	NPCs					
SNS/NE	α-AR and β-AR	ERK1/2 signaling pathway; PKA signaling pathway		Human IVD tissue and murine IVDD models	Unclear	[147]
NPY	Y2R	IL-1β pathway		Rat NPCs	Proliferation↑; IL-1β-induced cell apoptosis, IL-1β-induced matrix degradation↓	[20]
VIP	NA	NA		Human NPCs	Cell viability, expression of aggrecan and col2a1↑; Expression of pro-apoptotic (<i>Bax</i>) and catabolic genes (<i>MMP-3/13</i>) and inflammation-related genes↓	[167]
HSCs						
SNS	β2-AR and β3-AR	NA		Adrb2 ^{-/-} , Adrb3 ^{-/-} mice	Proliferation↑; Skews HSCs toward anti-inflammatory myeloid cells↑	[148]
NPY	Y1R	NA		Ly22-cre, 2.3-κB col1a1-cre, and Y1 ^{fl/fl} mice	Hematopoietic stem/progenitor cell mobilization↑	[153]

↑ Upregulation; ↓ Downregulation. NA. Not applicable; SNS. Sympathetic nervous system; NE. Norepinephrine; AR. Adrenergic receptor; OA. Osteoarthritis; AP-1. Activator protein 1; Jun-B. Jun B proto-oncogene; IL. Interleukin; MMP. Matrix metalloproteinase; GAG. Glycosaminoglycan; Sirt6. Sirtuin 6; miR-125. MicroRNA-125; Y2R. Neuropeptide Y receptor type 2; NPY. Neuropeptide Y; mTORC1. Mechanistic target of rapamycin complex 1; SMAD. Sma and Mad related protein; Runx. Runt-related transcription factor; ERK. Extracellular signal-regulated kinase; PKA. Protein kinase A; IVD. Intervertebral disc; IVDD. Intervertebral disc degeneration; VIP. Vasoactive intestinal peptide; Bax. Bcl-2-associated X protein; NPCs. Nucleus pulposus cells; HSCs. Hematopoietic stem cells

cyclin D1. In contrast, under chronic stress or inflammatory conditions *in vivo*, persistently elevated NE levels enhance RANKL expression and osteoclastogenesis, thereby driving bone resorption. This hypothesis can be tested using *in vivo* models comparing acute low-dose and chronic high-dose NE stimulation in combination with β 2-AR blockade to determine whether β 2-AR signaling undergoes a time- and intensity-dependent functional shift.

The PSNS and its neurotransmitter ACh exert a protective effect on bone homeostasis. Epidemiological studies have shown that nicotine affects bone metabolism via ACh receptors, with low doses stimulating osteogenesis and high doses inhibiting bone remodeling, which may explain the association between smoking, decreased bone mass, and an increased fracture risk [175,176]. Moreover, ACh regulates bone remodeling through both nAChR and mAChR, helping to maintain peak bone mass in adult mice [99,103,177].

Additionally, in an ovariectomized rat model, the blockage of Y1Rs significantly improved the bone microstructure, upregulated the osteogenic markers runt-related transcription factor 2 (Runx2) and OPG, and simultaneously reduced RANKL and MMP-9 levels [15]. Furthermore, the ECS also plays a role in bone metabolism, with activation of CB1 receptors tending to promote osteoclast activity and inhibit osteogenesis, whereas CB2 receptor activation tends to protect bone structure and maintain bone homeostasis [178]. Within this neuroendocrine framework, leptin, which is secreted by adipocytes, regulates food intake and energy metabolism through leptin receptors in the central hypothalamus [60,179–181] and influences bone formation and resorption via neural pathways [182]. Mechanistically, leptin increases sympathetic activity in glucose-sensitive neurons in the ventromedial hypothalamus, which increases NE release and downregulates the expression of the osteoblast proto-oncogene c-Myc. This process results in cell cycle arrest at the G1 phase, inhibiting osteoblast proliferation [59,100]. In addition, leptin-regulated sympathetic signaling promotes bone resorption by inducing RANKL expression in osteoblast progenitors via *Adrb2* and *ATF4* phosphorylation. Consistently, β 2-receptor knockout mice exhibit high bone mass [115], supporting a role for leptin-SNS signaling in bone loss. In contrast, several studies have demonstrated direct peripheral effects of leptin on bone cells. For example, leptin inhibits osteoclast generation in cultures of human peripheral blood mononuclear cells, possibly through interaction with soluble RANKL and increased OPG expression [61]. Moreover, leptin synergizes with 25(OH)D₃ to promote osteogenic differentiation of rat MSCs [183]. These findings suggest that leptin may act locally to enhance

bone formation and increase bone mass, thereby potentially reducing the risk of OP. Clinical studies have further examined the association between leptin and bone metabolism. In a study involving 121 healthy postmenopausal women, baseline leptin levels were positively correlated with spinal and hip bone mineral density (BMD) and were associated with reduced bone resorption [C-terminal telopeptide of type I collagen (CTX) levels decreased by 38%] and decreased bone formation markers [osteocalcin (OC) levels decreased by 21%] [184]. Even after adjusting for body mass index (BMI) or fat mass, the negative correlation between leptin and CTX levels persisted, indicating that leptin may be an independent factor involved in the peripheral suppression of bone resorption. In another cohort study of women, leptin levels were positively correlated with PTH levels, negatively correlated with 25-OH vitamin D levels, and strongly correlated with BMI [185]. More importantly, the classic “secondary hyperparathyroidism” phenomenon, in which a low vitamin D level is associated with high PTH levels, was observed only in the high leptin group. These interactions suggest that leptin may simultaneously suppress bone resorption and modulate the PTH response, thereby influencing bone metabolism under conditions of vitamin D deficiency. Therefore, targeting the inhibition of leptin secretion or production may serve as a potential therapeutic strategy. It could also aid in risk assessment and drug management for postmenopausal women with OP, providing a more accurate way to identify high-risk women and guide early intervention.

Emerging human clinical studies also provide preliminary evidence for other ANS-related interventions that aim to modulate bone metabolism. A case series involving postmenopausal women with bone loss revealed that oral cannabidiol (100–300 mg/d for 12 weeks) was well-tolerated and associated with reductions in bone resorption and formation markers, suggesting potential bone-protective effects [186]. More direct evidence was obtained from human studies on β -blockers. In a cohort study of 248 subjects and a randomized trial involving 155 postmenopausal women, β 1-selective blockers (atenolol and nebivolol) improved the bone microarchitecture, reduced serum CTX levels, and increased the distal radius BMD, whereas the nonselective β -blocker propranolol showed no comparable effects [187]. These findings suggest that bone-protective effects depend on receptor selectivity and may reflect species-specific differences in adrenergic regulation. Another clinical study involving 944 women revealed that the use of β -blockers was associated with higher femoral neck and lumbar spine BMD, a lower risk of fractures, and a better trabecular structure [188]. Consistently,

a nationwide case-control study in Denmark investigated the relationship between β -blocker use and fracture risk, and revealed that these drugs significantly reduced the fracture risk, particularly for hip fractures [189], supporting the efficacy of SNS inhibition in reducing bone resorption and the fracture risk.

In early postmenopausal women, the Leu7/Pro7 polymorphism of the NPY signaling gene was positively correlated with the femoral neck BMD. Five-year follow-up revealed that Leu7/Pro7 carriers in the non-hormone replacement therapy (non-HRT) group had less BMD loss, whereas HRT intervention did not significantly affect changes in the BMD of patients with this genotype [190]. In addition, patients with pheochromocytoma (a condition causing excessive catecholamine secretion and SNS overstimulation) had a 2.9% decrease in the lumbar spine trabecular bone score, reduced bone mass, and elevated levels of bone resorption markers. Urinary NE levels were negatively correlated with the lumbar spine bone microstructure and exhibited a dose-response relationship [191]. NPY may promote bone formation by regulating osteoblast activity and maintaining bone microstructure, whereas excessive SNS activation (elevated NE levels) accelerates osteoclast-mediated bone resorption and damages bone microstructure. Together with the above clinical data, interventions targeting SNS activity or NPY signaling may not only modulate the local balance between bone formation and resorption but also optimize bone homeostasis within the context of systemic neuro-endocrine regulation. Furthermore, OP patients may simultaneously experience ANS dysfunction. A prospective controlled trial revealed that OP patients exhibited increased sympathetic activity and decreased parasympathetic activity, which could further affect cardiac function [192].

Overall, OP involves not only abnormal bone metabolism but also systemic autonomic dysfunction, so interventions should aim to coordinate sympathetic and parasympathetic functions and their effects on other organs, rather than merely suppressing sympathetic activity.

Osteoarthritis

OA, which is characterized by cellular stress and ECM degradation, is one of the most prevalent joint disorders worldwide [193]. As of 2020, osteoarthritis affected approximately 595 million individuals worldwide, representing 7.6% of the global population, and cases are projected to approach or exceed one billion by 2050 due to population growth and ageing [194]. Unfortunately, an effective strategy to prevent or reverse OA is still unavailable. The standard treatment involves a combination of pharmacological and

nonpharmacological therapies to alleviate symptoms, with joint replacement reserved as the last resort [195-197]. Although these treatments partially relieve symptoms and improve function, the effectiveness of pharmacological therapies remains limited, and these treatments can lead to adverse effects such as cardiovascular disease, gastrointestinal bleeding, and renal impairment [198,199]. Furthermore, joint replacement carries risks, including catastrophizing, unrealistic expectations, and pain sensitization [198].

Recently, the potential role of the ANS in pathological changes associated with OA through neurotransmitter-receptor interactions has attracted increasing attention. Many studies have shown that the SNS is a crucial mediator of pathological changes in multiple joint tissues during the progression of OA [10,131,134,200]. In a temporomandibular joint (TMJ)-OA rat model, abnormal occlusion activated the SNS, which further induced osteoclast activation and accelerated cartilage and bone degeneration [201]. Interestingly, propranolol (a β -AR antagonist) effectively inhibited this effect. Additionally, the PSNS is believed to play an important role in cartilage degeneration. Notably, nicotine activates the $\alpha 7$ -nicotinic acetylcholine receptor ($\alpha 7$ -nAChRs) on chondrocytes, effectively preventing cartilage degeneration and reducing proteoglycan loss [202,203]. These findings highlight the potential therapeutic benefits of targeting specific receptor pathways in the regulation of cartilage degeneration. However, considering the potential damage to other organs caused by nicotine and similar agents, identifying an effective, nontoxic dose or alternative receptor agonist with greater safety and specificity would be beneficial.

Subchondral bone remodeling abnormalities are considered key factors involved in the progression of OA [204]. Specifically, subchondral bone sclerosis affects its ability to absorb and distribute mechanical loads, thereby accelerating cartilage degeneration [205]. Notably, increased SNS activity has been observed during OA progression, influencing both subchondral bone remodeling and cartilage degeneration [206]. NE-mediated SNS signaling can accelerate osteoblast senescence and disrupt subchondral bone homeostasis in aging mice [136]. In a mouse model of knee OA, inhibition of sympathectomy (SYM) or knockout of $\beta 2$ -AR (*Adrb2*^{-/-}) resulted in increased subchondral BMD, possibly because $\beta 2$ -AR activation inhibited osteoblast function while promoting osteoclast activation [131,207]. Evidence across different OA models consistently indicates that SNS/ $\beta 2$ -AR signaling suppresses osteoblast activity and promotes osteoclast activation, leading to subchondral bone loss, with differences among studies mainly reflecting variations in experimental

models and intervention strategies.

Other sympathetic neuropeptides, such as VIP, have been shown to exert strong anti-inflammatory and immunomodulatory effects on cartilage degeneration and synovial inflammation [208,209]. In a rheumatoid arthritis (RA) mouse model, VIP treatment significantly alleviated arthritic symptoms. Clinical observations revealed that the joint swelling and inflammation scores were markedly lower in the VIP treatment group than in the control group. Specifically, VIP treatment improved pathological changes in joints by downregulating the levels of proinflammatory cytokines such as TNF- α , IL-1, and IL-6, and inhibiting T helper (Th)1 cell responses [e.g., IL-12/interferon- γ (IFN- γ) production] [210,211]. Additionally, VIP promoted the differentiation of Th2 cells, enhancing their anti-inflammatory effects [210,211]. These findings provide important insights into the potential immunomodulatory effects of VIP, particularly for applications in rheumatoid diseases.

Recent studies have emphasized the role of NE in OA pathogenesis, showing that NE can regulate the metabolism and inflammatory response of human chondrocytes [18,183]. Specifically, at a high concentration (10^{-6} mol/L), NE activates β -AR, reverses the IL-1 β -induced increase in IL-8 and MMP-13, and restores the synthesis of type II collagen and GAGs, indicating potential anti-inflammatory effects. However, at a lower concentration (10^{-8} mol/L), NE induces apoptosis via the α 1-AR signaling pathway [18]. Notably, the effects of NE are not limited to chondrocytes. In human MSCs and chondroprogenitor cells, NE-mediated β 2-AR signaling may inhibit cartilage regeneration by suppressing the deposition of sGAGs and type II collagen [73,212,213]. These findings suggest that sympathetic NE signaling through β -AR may transiently suppress inflammation, yet persistent or imbalanced activation in degenerative cartilage shifts signaling toward apoptosis or impaired matrix synthesis. In contrast, vagus nerve stimulation (VNS)-mediated vagal activation primarily modulates systemic and central inflammation, potentially reducing pain and inflammatory burden without directly correcting cartilage degeneration. Furthermore, selective serotonin and NE reuptake inhibitors (SNRIs), such as milnacipran and duloxetine, exert significant analgesic effects during OA treatment. In a clinical study of the use of milnacipran in RA patients, the pain intensity was significantly reduced by 1.14 points after 6 weeks in a subgroup with a joint swelling count ≤ 1 , compared with that in the placebo group [214]. This result supports the potential of sympathetic neurotransmitter accumulation in chronic pain management.

In addition, VNS, a direct method of modulating the ANS,

has been shown to exert anti-inflammatory and analgesic effects on patients with RA. VNS modulates the vagus nerve to reduce peripheral and central inflammatory responses, representing a new therapeutic approach for OA. Both invasive and transcutaneous VNS stimulation significantly alleviate OA symptoms, including pain and inflammation [215]. Transcutaneous auricular VNS (tVNS) has therefore emerged as a potential therapeutic strategy for knee OA [216], possibly by correcting the reduced parasympathetic activity associated with the disease, although its precise mechanisms and effects on tissue degeneration require further investigation.

In summary, the ANS plays a crucial role in the complex processes of OA development and progression.

Fracture healing

A bone fracture refers to the disruption of bone integrity and continuity, typically caused by trauma or skeletal disease, and is often accompanied by localized pain, swelling, and functional impairment [217,218]. With the steady increase in human life expectancy, age-related and osteoporotic fractures have become increasingly common and have emerged as major contributors to chronic pain and long-term disability worldwide [219–221]. These injuries not only impair physical function but also negatively impact mental health [222]. Therefore, identifying and optimizing strategies to promote fracture healing has become a pressing issue [223].

Recently, the potential role of the SNS in fracture healing has garnered increasing attention [40,224]. In mice, the SNS forms a complex network widely distributed across cortical bone, trabecular bone, bone marrow, and periosteum, with the highest nerve density observed in areas of active bone formation, suggesting that the SNS may play a critical role in the early stages of fracture healing [25]. However, in sympathetic denervation experiments, mice with fractures exhibited a significant reduction in the trabecular bone volume and a marked decrease in bone mechanical strength, both in fractured and nonfractured bones [40,225,226]. This phenomenon highlights the importance of the SNS in bone homeostasis, particularly in the late stages of fracture healing, where the absence of sympathetic innervation not only delays callus maturation [227] but also significantly impairs mechanical stability [228].

Moreover, NE primarily promotes fracture healing through interactions with its receptors. Research has demonstrated that in a mouse model of femoral fractures and traumatic brain injury (TBI), the excessive sympathetic state induced by TBI enhances fracture repair via the NE- β 2-AR signaling pathway [229–231]. These findings suggest that TBI may accelerate

fracture healing by activating the SNS, providing new clinical insights for treating traumatic fractures. However, the effect of the SNS on fracture healing is not entirely beneficial. A study using a rat model of mandibular distraction osteogenesis with transection of the cervical sympathetic trunk has also shown that the NE- β 3-AR signaling pathway negatively affects fracture healing under certain conditions, possibly by downregulating the expression of osteogenic genes such as *ALP*, *Runx2*, and *OCN* in MSCs, thereby inhibiting fracture repair [82]. Taken together, the effects of SNS signaling in fracture healing are determined by receptor subtypes and activation patterns. These results from animal models highlight the need for higher-quality human clinical trials to evaluate the therapeutic potential of ANS modulation in fracture healing.

A study using a chronic post-fracture pain mouse model has shown that enhancing parasympathetic signaling through nicotine administration, which augments the cholinergic system, effectively alleviates postoperative pain [232]. This suggests that manipulating ANS may play a crucial role in managing pain following traumatic fractures. Additionally, in a mouse femoral closed fracture model, significant amounts of sensory and sympathetic nerve fiber sprouting were observed at the nonhealed fracture site. The nerve fiber density increased, and structures resembling neuromas formed. This abnormal nerve growth not only poses a potential risk factor for fracture healing but also may contribute to ectopic skeletal pain [221]. In line with these findings, a randomized, double-blind study demonstrated that preoperative sympathetic block significantly reduced pain in patients undergoing upper limb orthopedic surgery, further emphasizing the importance of autonomic modulation in pain management [233].

The role of the SNS in bone repair has become a focal point of research. For instance, research has shown that wild-type mice subjected to fracture exhibit trauma-specific hyperinsulinemic stress responses and a decrease in *OCN* levels, which accelerates fracture healing. Leptin-deficient mice, however, lose the specificity of *OCN* changes, resulting in impaired fracture healing [234]. This observation aligns with previous research that underscores the promotive effects of the SNS on fracture healing [231]. Additionally, TBI is significantly associated with accelerated fracture healing [235]. Research by Wei *et al.* [236] revealed a positive correlation between serum leptin levels and callus volume at fracture sites in TBI patients. The marked increase in leptin concentration between weeks 4 and 12 post-trauma suggests that leptin may facilitate bone mineralization and osteoblast differentiation into osteocytes through peripheral effects, thereby accelerating fracture healing.

In addition to NE, NPY has garnered increasing attention for its role in bone repair, with several studies confirming its functional involvement [80,237,238]. Under physiological conditions, NPY-positive fibers are predominantly localized in blood vessels, with a sparse distribution in the periosteum [239,240]. However, following a fracture, the number of NPY-positive fibers at the injury site significantly increases [237]. These findings suggest that NPY may play a key regulatory role in fracture healing. Animals with *Y1R* knockdown exhibit delayed early fracture healing, characterized by smaller callus volume, reduced mechanical strength, and insufficient vascularization [238,241]. Conversely, *Y2R* knockout can increase the number of mesenchymal precursor cells in mice, increase osteogenic potential, and ultimately lead to an increased bone mass [33,242]. The discrepancy in these findings may be attributed to differences in experimental design or the diversity of NPY receptor subtypes. Therefore, further research is needed to clarify the specific mechanisms of NPY in fracture healing. In mice with sympathetic nerve depletion induced by 6-OHDA, the femoral bone density, microstructure, and mechanical strength are significantly decreased, and fracture healing is markedly suppressed. However, local treatment with VIP led to significant improvements in bone microstructure and mechanical performance, with restored expression of osteogenic markers, such as *OCN* and *OPN* [40].

Overall, the SNS appears to exert a predominantly beneficial effect on traumatic fracture healing. Moderate sympathetic activation, particularly via β 2-adrenergic signaling, promotes osteogenic differentiation and callus formation. In addition, leptin-related pathways are associated with increased callus volume and accelerated mineralization. Despite these promising findings, limitations still exist. Most studies have been conducted in animal models, for which no specific drugs targeting fractures through ANS modulation are yet available. Additionally, the optimal timing for treatment remains uncertain. For instance, the efficacy of reboxetine and VIP manifests primarily in the later stages of fracture healing, but the mechanisms underlying their early effects remain unclear.

Intervertebral disc degeneration

IVDD is defined as a progressive condition characterized by structural and functional deterioration of the disc, which is driven mainly by aging and repeated mechanical stress [243,244]. IVDD has become a major global public health concern. In advanced stages, it often results in a wide range of disabling symptoms, such as chronic low back pain [245,246],

muscle weakness, reduced mobility, bowel or bladder dysfunction, and sensory disturbances in the extremities [247]. Globally, low back pain affected approximately 619 million people in 2020 and remained the leading cause of years lived with disability, with the number of prevalent cases projected to increase to 843 million by 2050 [194]. However, current therapies focus primarily on symptom relief and are largely ineffective at halting or reversing the degenerative process. Therefore, elucidating the underlying mechanisms of IVDD is crucial. Previous studies identified sympathetic nerve fibers and ARs in both healthy and degenerated disc tissues [147,248], suggesting that the SNS might be involved in the pathogenesis and progression of IVDD.

In healthy intervertebral discs, sympathetic nerve fibers are located primarily around the annulus fibrosus, often in proximity to blood vessels [249,250]. A study of rat cervical intervertebral discs has shown that sympathetic nerve fibers comprise approximately 20.4% of the total nerve fibers [251]. These findings suggest that SNS plays a role in the physiological function of the disc, possibly by regulating blood flow and cellular activity to help maintain normal disc metabolism. However, as the disc degenerates, a significant increase in the number of sympathetic nerve fibers occurs, and these fibers invade regions that were previously devoid of innervation, such as the inner annulus and even the nucleus pulposus [167,251]. This change is not only pathological but also a hallmark of degenerative disc changes, suggesting that the SNS may accelerate the degenerative process. Increased AR expression appeared to be involved in pathological processes during IVDD. On the one hand, it is associated with catabolic activity and pain signaling mediated by neurotransmitters such as NE [252]. On the other hand, AR activation might exacerbate disc degeneration by enhancing hypertrophic changes in NPCs [167].

NPY and VIP are also increasingly recognized for their roles in IVDD. It has been demonstrated that the accumulation of NPY is significantly increased in degenerated rat intervertebral discs compared with naturally aging discs [19]. These observations suggest that the excessive accumulation of NPY may serve as a hallmark of disc degeneration. Dysregulation of the neuropeptide Y-Y receptor (NPY-YR) axis could be a major driving factor for degenerative changes in the disc, particularly in processes involving inflammatory pain, disc cell apoptosis, and ECM degradation [253,254]. Targeting this axis may significantly slow the degenerative process of the disc and alleviate the associated clinical symptoms, although clinical trials have not yet been conducted on neuroregulation-based treatments for IVDD.

Staining of human and mouse intervertebral disc tissues has shown that nearly all types of ARs are present in intervertebral discs at various stages of degeneration [147]. These findings suggest that the SNS plays an important role in the pathogenesis of IVDD, with different AR subtypes potentially playing distinct roles in the degenerative process. Brenneis *et al.* [252] further analyzed the expression of ARs in degenerative human intervertebral discs and correlated these findings with clinical parameters such as the Pfirrmann grade. The results showed that the expression of $\alpha 1A$ -AR, $\alpha 2A$ -AR, and $\beta 2$ -AR was significantly correlated with the Pfirrmann grade, suggesting the potential of ARs as prognostic markers for IVDD. Specifically, changes in the expression of these receptors reflect the severity of the degenerative process. However, the limitation of this conclusion lies in its reliance on correlation analysis, with a lack of mechanistic validation.

An *in vivo* study in a rat model has revealed the negative effect of the NPY-Y1R signaling pathway on the degenerative process [19]. However, research on human lumbar intervertebral discs suggests that NPY, under certain conditions, may exhibit a bidirectional regulatory effect by promoting disc cell proliferation. NPY upregulates the expression of cyclin D1 and proliferating cell nuclear antigen (PCNA), while downregulating the expression of pro-apoptotic proteins such as Bax and caspase-3/8, thereby reducing IL-1 β -induced apoptosis [20]. These results indicate that NPY does not exert a solely pro-degenerative effect; instead, its biological impact may depend on the receptor subtype expression and species differences. Additionally, VIP-positive sympathetic nerve fibers have been detected in degenerative rat intervertebral disc tissues [145]. Further studies have shown that the expression of VIP receptors in human intervertebral discs is negatively correlated with the severity of IVDD. Exogenous VIP administration improved IL-1 β -induced NPC apoptosis and inflammation. VIP delays the progression of IVDD through the FGF18/FGFR2-mediated Akt signaling pathway [12]; therefore, targeting the VIP signaling pathway may have therapeutic potential for slowing inflammation and apoptosis in IVDD.

In summary, the significant correlation between the expression of ARs, VIP receptors, and NPY in patients with IVDD and clinical parameters supports their potential as biomarkers. However, as a potential therapeutic target for fracture treatment, the safety and efficacy of modulating the ANS still require validation through high-quality clinical trials.

Other musculoskeletal pathologies

Frozen shoulder is characterized by chronic aseptic

inflammation and fibrosis of the soft tissues surrounding the shoulder joint, resulting in severe pain and restricted active and passive range of motion [255,256]. A case-control study revealed that patients with frozen shoulder exhibited significantly greater ANS dysfunction compared to healthy controls [257]. This study directly included human subjects and demonstrated that ANS abnormalities were associated with shoulder tissue fibrosis and pain, indicating significant clinical relevance.

Craniofacial bone defects involve the loss of major facial and cranial bones due to infection, trauma, tumors, or genetic factors [32,258]. A rat model of mandibular distraction osteogenesis with cervical sympathetic trunk transection demonstrated increased new bone formation following sympathetic denervation, suggesting that the SNS may negatively regulate new bone formation during distraction osteogenesis [259].

Adolescent idiopathic scoliosis (AIS) is a multifactorial three-dimensional spinal deformity that mainly affects children around puberty and is characterized by low body weight, reduced BMI, decreased bone mass, and increased arm span [260,261]. A Hong Kong, China study of 58 girls with AIS revealed elevated plasma adrenaline and NE levels, which negatively correlated with body weight, BMI, and BMD [260]. These findings suggest that SNS overactivation may drive the “low weight+low bone mass” phenotype of AIS patients, highlighting the potential of SNS inhibition (e.g., β -blockers) to improve bone mass in AIS patients.

Delayed onset muscle soreness is typically observed after unaccustomed or eccentric exercise and is characterized as a transient skeletal muscle condition [262]. Its development is closely associated with mechanical microtrauma, inflammation, and the leakage of enzymes and electrolytes [263,264]. A randomized controlled trial by Fleckenstein *et al.* [265] confirmed that stellate ganglion block, by temporarily inhibiting the SNS, significantly reduced the expression of inflammation markers such as cell-free DNA and alleviated delayed-onset muscle soreness-related pain.

Bone tumors are categorized into primary and secondary types, with secondary bone tumors referred to as metastatic tumors. Due to its unique activity and regenerative potential, the skeleton has become the third most common site for cancer metastasis, following the lungs and liver [266,267]. The ANS plays a crucial role in certain symptoms of bone tumors, such as cancer-induced bone pain (CIBP). For example, in a rat model of CIBP, the $\alpha 7$ -nAChR agonist PNU-282987 produced dose-dependent analgesic effects on the spinal cord [266,267], indicating that spinal $\alpha 7$ -nAChR activation is

effective for the relief of bone cancer pain.

Clinical studies suggest that β -blockers can reduce disease-specific and overall mortality in multiple myeloma (MM) patients, suggesting that SNS activation may worsen the prognosis of MM [268,269]. Some retrospective data also indicate that high expression of cholinergic receptor genes correlated with poor survival outcomes for MM patients [268,270]. However, increased receptor gene expression does not necessarily imply enhanced downstream biological effects, as receptor expression levels do not always correlate with functional outcomes, underscoring the need for functional validation. AR antagonists, such as propranolol and carvedilol, decrease the viability of both human and canine osteosarcoma cell lines in a dose-dependent manner. Short-term use of these drugs does not significantly affect clonogenic survival, but prolonged low-dose carvedilol treatment increases osteosarcoma cell death after radiation exposure [271]. These findings suggest that carvedilol could be a potential adjunct for radiotherapy in individuals with osteosarcoma, warranting further exploration of its antitumor effects. Ewing sarcoma (ES) has a poor prognosis and is closely linked to metastasis, tumor hypoxia, and chromosomal instability (CIN). A study has shown the hypoxia-induced NPY/Y5R axis stimulates excessive RhoA activation, leading to the formation of polyploid ES cells with high CIN, bone invasiveness, and drug resistance. Blocking Y5R prevents polyploidization and bone metastasis, suggesting that targeting the NPY/Y5R/RhoA axis could inhibit CIN and ES progression [272]. Additionally, persistent expression of NPY and Y5R in ES tumors increases serum peptide levels, which are correlated with poor prognosis. The NPY/Y5R axis drives ES cell motility through RhoA activation, further supporting its critical role in ES metastasis [273]. Breast cancer cells have a strong tendency for bone metastasis, and the SNS facilitates this process by promoting bone resorption. Sympathetic neurotransmitters activate α - and β -ARs, thereby enhancing angiogenesis, immune evasion, and bone metastasis in breast cancer [274]. Campbell *et al.* [275] also indicated that SNS activation (via severe psychological stress and depression) influences the host bone marrow stroma through neurohormones, promoting the colonization of MDA-231 breast cancer cells in mouse bones. Furthermore, propranolol inhibits breast cancer bone metastasis. The upregulation of IL-6 and the JAK/STAT3 signaling pathway may be a key mechanism by which chronic stress promotes bone metastasis in patients with breast cancer, and propranolol effectively inhibits this pathway [276]. Population-based studies also support the use of β -blockers in managing bone metastasis associated with breast cancer [277],

and the potential for sympathetic receptor intervention in breast cancer bone metastasis is gradually gaining recognition (Fig. 4, Table 4) [12,15,19,31,40,88,131,136,148,202,207,226,231,232,238,259,265,272,278,279].

Conclusion and future perspective

The ANS, through its sympathetic and parasympathetic branches, exerts regulatory control over various cell types [8,94], particularly those associated with bone, joints, and

intervertebral discs, including MSCs, osteoblasts, osteoclasts, NPCs, and chondrocytes. By releasing neurotransmitters such as NE, ACh, NPY, and VIP, the ANS modulates cellular behaviors including proliferation, differentiation, migration, and functional activity, thereby influencing the development, metabolism, remodeling, and repair processes of skeletal tissues. In the context of bone-related disorders, dysfunction of the SNS and PSNS has frequently been linked to dysregulated bone metabolism, as observed in conditions such as OP, OA,

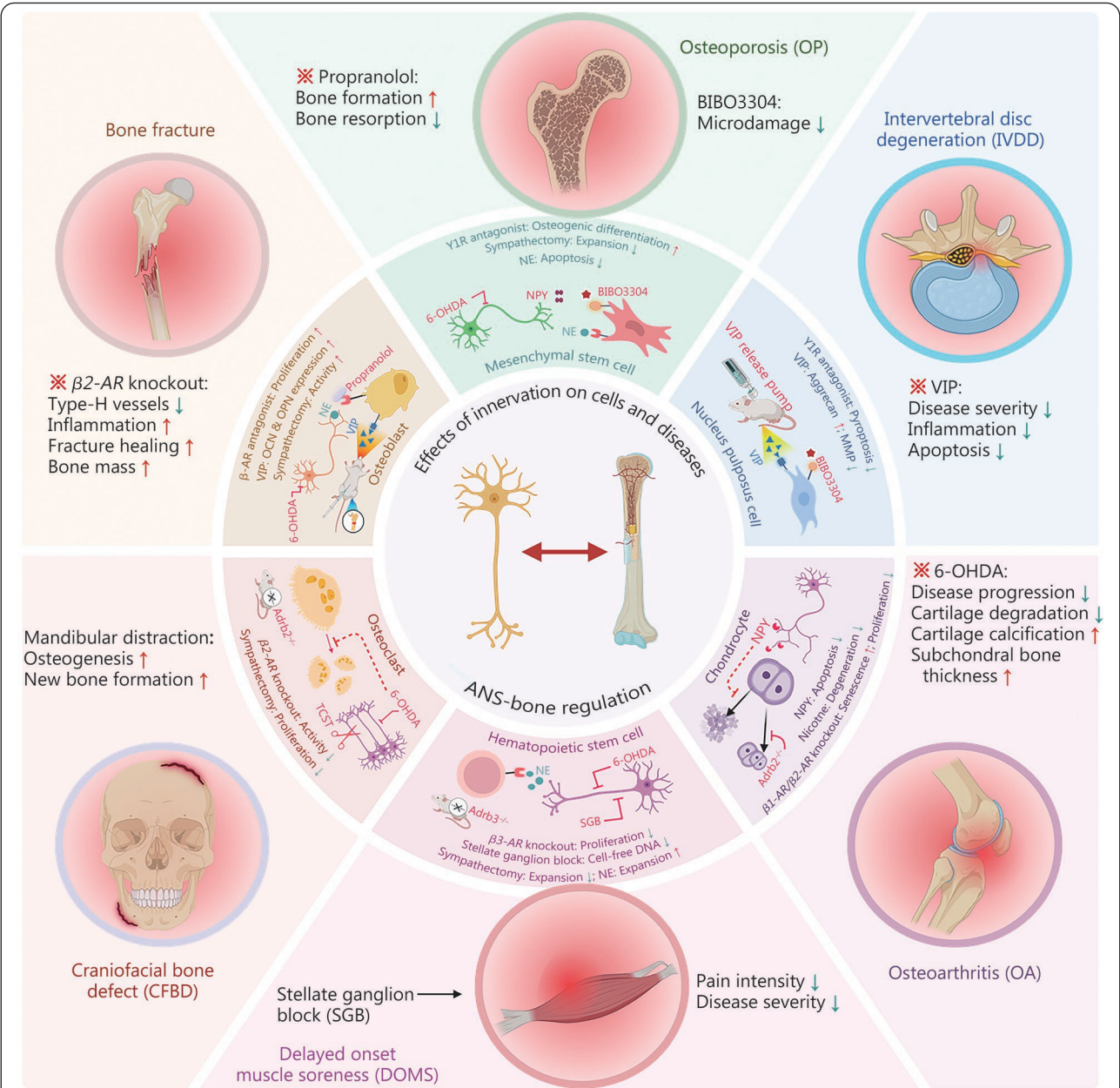


Fig. 4 Schematic diagram showing the effects of different types of autonomic nervous interventions or therapies on various bone-related cells and their therapeutic effects on various musculoskeletal disorders.

Created with BioRender.com. $\uparrow$ Upregulation; $\downarrow$ Downregulation; $\times$ Interventions with significant regulatory impact on the autonomic nervous system. ANS. Autonomic nervous system; Y1R. Neuropeptide Y receptor type 1; NE. Norepinephrine; 6-OHDA. 6-hydroxydopamine; NPY. Neuropeptide Y; VIP. Neuropeptide Y; MMP. Matrix metalloproteinase; OCN. Osteocalcin; OPN. Osteopontin; Adrb3. Adrenergic receptor beta; TCST. Transection of cervical sympathetic trunk; DNA. Deoxyribonucleic acid

Table 4 Therapeutic effects of ANS interventions in bone diseases

Disease types	Disease models	ANS intervention strategies	Targets for intervention	Bone cell lineage involvement	Therapeutic strategies	Cell effects	Disease effects	References
Osteoporosis (OP)	Tibia fracture models in mice with ovariectomy (OVX)-induced postmenopausal OP	Propranolol (a nonselective β -AR antagonist)	β -AR	Osteoblasts; Osteoclasts	Combined PTH and propranolol	Osteogenesis $\uparrow$; Osteoclastogenesis $\downarrow$	OP severity $\downarrow$; Osteoporotic fracture healing $\uparrow$	[88]
	Bone microdamage model in rats with OVX-induced postmenopausal OP and <i>in vivo</i> fatigue loading	BIBO3304 (a Y1R antagonist)	Y1R	BMSCs	BIBO3304	Osteogenesis, Runx2 & OCN $\uparrow$; RANKL/OPG ratio $\downarrow$	OP severity, microdamage $\downarrow$	[15]
	Femoral fracture models in rats with OVX-induced postmenopausal OP	Chemical SYMX with 6-hydroxydopamine (6-OHDA)	Sympathetic nerves	NA	SYMX	NA	Bone volume $\uparrow$	[226]
	Rat OVX-induced postmenopausal OP model	Propranolol (a nonselective β -AR antagonist)	β -AR	Osteoblasts	Propranolol	Osteogenesis $\uparrow$	Mineral density $\uparrow$; Leptin and leptin receptor level $\uparrow$ →bone formation $\uparrow$; bone resorption $\downarrow$	[278]
Osteoarthritis (OA)	Naturally aging mouse model of OA	Propranolol; β 1-AR knockout; depletion of TH $^{+}$ sympathetic nerves (oxidized dopamine (6-OHDA) or guanethidine)	β -AR; β 1-AR; TH $^{+}$ sympathetic nerves	Chondrocytes	Propranolol; β 1-AR knockout; SYMX	Propranolol: β 1-AR and β 2-AR $\downarrow$, Sirt6 $\uparrow$, miR-125 $\uparrow$; β 1-AR knockout: MMP-13 $\downarrow$, Sirt6 $\uparrow$; SYMX: MMP-13 $\downarrow$	Propranolol: aging-related OA severity $\downarrow$; β 1-AR knockout: aging-related OA severity $\downarrow$; SYMX: aging-related OA $\downarrow$	[136]
	Monosodium iodoacetate (MIA)-induced knee joint OA mouse model	Nicotine (a nAChR potent agonist); Methyllycaconitine (MLA, α 7-nAChR antagonist)	α 7-nAChR	Chondrocytes	Nicotine; MLA	Nicotine: aggrecan loss $\downarrow$, degeneration $\downarrow$, MMP-9 $\downarrow$; MLA: aggrecan loss $\downarrow$, degeneration $\uparrow$, MMP-9 $\uparrow$	Nicotine: OA-induced mechanical allodynia $\downarrow$, MIA-induced cartilage degradation $\downarrow$; MLA: OA-induced mechanical allodynia $\uparrow$, MIA-induced cartilage degradation $\uparrow$	[202]
	A mouse model of temporomandibular joint (TMJ)-OA induced by unilateral anterior crossbite	Conditional deletion of β 2-AR in the nestin+MSCs	β 2-AR	MSCs; Chondrocytes; Osteoclasts	Conditional deletion of β 2-AR in MSCs	Osteoclast: hyperfunction $\downarrow$; Chondrocytes: cartilage thickness, cell density, proteoglycan-positive area, collagen II, aggrecan, MMP-13, MMP-3, calcified cartilage, ALP-positive area, ALP mRNA $\downarrow$	Cartilage degradation, calcified cartilage thickening, subchondral bone loss $\downarrow$	[279]
	The OA model of wild-type and SYMX mice induced by destabilization of the medial meniscus (DMM)	SYMX by intraperitoneal injections of 6-OHDA	TH $^{+}$ sympathetic nerves	Chondrocytes; Osteoblasts; Osteoclasts	SYMX	Chondrocytes: no influence on β 2-AR; Osteoclast: activity $\uparrow$; Osteoclast: activity $\downarrow$	Cartilage calcification, subchondral bone thickening $\uparrow$	[131,207]
	The right knee OA model of 8-week-old male mice induced by DMM	Intra-articular injection of NPY	NPY1R; NPY2R	Chondrocytes	BIBO3304; BIBO246	BIBO246: Col10a1 $\downarrow$, MMP-13 $\downarrow$, ADAMTS-5 $\downarrow$, p56-positive chondrocytes $\downarrow$, apoptosis $\downarrow$, hypertrophy $\downarrow$	BIBO246: NPY-induced cartilage degradation and fibrillation $\downarrow$; BIBO3304: no effect on NPY-induced cartilage degradation and fibrillation	[31]

(Continued)

Disease types	Disease models	ANS intervention strategies	Targets for intervention	Bone cell lineage involvement	Therapeutic strategies	Cell effects	Disease effects	References
Bone fracture	Tibia fracture mouse model of chronic posttraumatic pain with features of complex regional pain syndrome	Chemical SYMX by intraperitoneal injections of 6-OHDA; Inhibition of sympathetic outflow with Lofexidine (an $\alpha 2$ -AR agonist); Parasympathetic augmentation with nicotine	TH ⁺ sympathetic nerves; $\alpha 2$ -AR; nAChR	NA	SYMX; Lofexidine; Nicotine	NA	SYMX, nicotine, lofexidine: fracture-induced nociceptive sensitization and inflammation↓	[232]
	Murine femoral osteotomy combined with cortical impact brain injury/traumatic brain injury (TBI) model	A hyperadrenergic state induced by TBI	Sympathetic nerves; $\beta 2$ -AR	Osteoblasts; Osteoclasts; Periosteal cells	$\beta 2$ -AR knockout; propranolol; atenolol; formoterol	$\beta 2$ -AR knockout: osteogenesis↑, osteodlastogenesis↓; $\beta 2$ -AR knockout: VEGF-A↓ in periosteal cells, hypoxia-inducible factor 1 α ↓ in periosteal cells	$\beta 2$ -AR knockout: bone mass in the unfractured skeleton↑, fracture healing↓; Propranolol & formoterol: fracture nonunion↑, type-H vessels density↓; Atenolol: no effect on fracture	[231]
	Mouse TBI combined with the femur fracture model	Chemical SYMX with 6-OHDA; $\beta 2$ -AR and $\beta 3$ -AR knockout	Sympathetic nerves; $\beta 2$ -AR; $\beta 3$ -AR	BMSCs; BHSCs; BMDMs	SYMX; $\beta 2$ -AR and $\beta 3$ -AR knockout; NE; Clenbuterol; BRL37344; Combined clenbuterol & BRL37344	SYMX: proliferation ↓ in BMSCs & BHSCs; SYMX: OCN, OSX, OCPs, TRAP ⁺ cells, anti-inflammation myeloid cells↓; NE: expansion ↑ in BHSCs; $\beta 2$ -AR knockout: M2 polarization ↓ in BMDMs; $\beta 3$ -AR knockout: proliferation ↓ in BHSCs; β -AR agonist: M2 macrophages↑, OCN↑	SYMX: TBI-accelerated fracture healing↓; β -AR agonist: fracture healing↑	[148]
	Mouse closed tibial fracture model	Germline Y1R knockout; Osteoblastic-specific Y1R knockout	Y1R	Chondrocytes; Osteoblasts	Germline Y1R knockout; Osteoblastic-specific Y1R knockout	Germline Y1R knockout: chondrocyte hypertrophy↑	Germline Y1R knockout: cartilage callus removal↓, hard callus formation↓→ early fracture healing↓; Osteoblastic-specific Y1R knockout: no effect on fracture healing	[238]
	Mouse femur transverse fracture model	Chemical SYMX with 6-OHDA	Sympathetic nerves	Osteoblasts	VIP	OCN, OPN↑	SYMX-impaired bone fracture healing↑	[40]
Intervertebral disc degeneration (IVDD)	Rat IVDD model established by percutaneous disc puncture	Needle puncture induces aberrant distribution of NPY in the degenerative disc	Sympathetic nerves	Nucleus pulposus cells (NPCs)	BIBO3304	Pyroptosis↓	Pyroptosis↓→ IVDD development↓	[19]
	Mice lumbar instability-induced lumbar IVDD model	The injection of exogenous VIP into mice with IVDD via a sustained-release pump	VIP2R	NPCs	VIP	ACAN↑, MMP-3↓	Lumbar instability-induced IVDD development↓	[12]

(Continued)									
Disease types	Disease models	ANS intervention strategies		Targets for intervention	Bone cell lineage involvement	Therapeutic strategies	Cell effects	Disease effects	References
Craniofacial bone defect (CFBD)	Rat bilateral transection of cervical sympathetic trunk (TCST), mandibular distraction osteogenesis model	Bilateral TCST		Sympathetic nerves	Osteoclasts	Transection of the sympathetic innervation	Bone mass, quantity of trabeculae↑	New bone callus maturity↑	[259]
Delayed onset muscle soreness (DOMS)	DOMS of the biceps muscle model	Stellate ganglion block (SGB)		Sympathetic nerves	Hematopoietic cells	SGB before exercise-induced DOMS (preventive); SGB after the induction of DOMS (rehabilitative)	cell-free DNA↓	DOMS severity↓, DOMS-related pain intensity↓	[265]
Ewing sarcoma	Orthotopic Ewing sarcoma xenograft model	Blocking Y5R		Y5R	SK-ES-1 cell line (human Ewing sarcoma cell line)	CRISPR/Cas9 NPY5R gene editing	Polyploid cell formation, chromosomal instability↓, and genomic stability of tumor cells↑	Bone metastasis, chemoresistance, disease progression↓	[272]

↑ Upregulation; ↓ Downregulation. NA. Not applicable; ANS. Autonomic nervous system; AR. Adrenergic receptor; PTH. Parathyroid hormone; Y1R. Neuropeptide Y receptor type 1; BMSCs. Bone marrow mesenchymal stem cells; Runx2. Runt-related transcription factor 2; MSCs. Mesenchymal stem cells; OCN. Osteocalcin; RANKL. Receptor activator of nuclear factor kappa-B ligand; OPG. Osteoprotegerin; SYMX. Sympathectomy; MMP. Matrix metalloproteinase; nAChR. Nicotinic acetylcholine receptor; MLA. Methyllycaconitine; mRNA. Messenger ribonucleic acid; ALP. Alkaline phosphatase; NPY. Neuropeptide Y; NE. Norepinephrine; BHSCs. Bone marrow hematopoietic stem cells; BMDMs. Bone marrow-derived macrophages; VIP. Vasoactive intestinal peptide; TH. Tyrosine hydroxylase; Sirt6. Sirtuin 6; OSX. Osterix; OCPs. Osteoclast precursors; TRAP. Tartrate-resistant acid phosphatase; Col10a1. Collagen type X alpha 1 chain; ADAMTS-5. A disintegrin and metalloproteinase with thrombospondin motifs 5; VEGF-A. Vascular endothelial growth factor A; ACAN. Aggrecan; NPY5R. Neuropeptide Y receptor Y5

traumatic fractures, and IVDD. This correlation appeared especially pronounced in age-related skeletal pathologies, highlighting an urgent need to elucidate the complex interplay between autonomic inputs, neurotransmitter signaling, and downstream cellular responses. With growing insights into the role of the ANS in bone homeostasis, neuromodulation-based strategies have emerged as promising therapeutic approaches for bone-related disorders.

Recent advances in both neuromodulatory devices and pharmacological interventions have demonstrated substantial potential. By finely tuning the activity of the SNS and PSNS, these strategies effectively modulated bone metabolism and enhanced bone repair and regeneration. For instance, VNS was reported to slow the progression of OA [215]. Pharmacological interventions, particularly highly selective β 1-AR antagonists, hold substantial translational promise for osteoporotic neuromodulation [88,108,280]. Nevertheless, off-target cardiovascular effects and suboptimal delivery efficiency continue to hinder their broader clinical application. Future therapeutic strategies should combine these sympathetic inhibitors with bone-targeted nanocarriers to maximize osteogenic benefits while circumventing systemic toxicity. Moreover, tVNS has emerged as a promising non-invasive strategy for OA [216]. Compared with systemic central analgesics (such as SNRIs) [214] and irreversible nerve ablation [131,207], tVNS offers a safer alternative. Mechanistically, it mitigates central pain sensitization via the cholinergic anti-inflammatory pathway while concurrently suppressing synovial inflammation and delaying cartilage degeneration. However, conventional fixed-stimulation protocols are hindered by unstandardized parameters and substantial inter-individual variability in baseline autonomic tone. Future strategies should focus on personalized, feedback-driven systems. By integrating objective biomarkers such as heart rate variability to dynamically adjust stimulation, this adaptive approach can optimize analgesic and joint-protective outcomes across diverse OA cohorts.

For fractures and IVDD, the localized delivery of autonomic neuromodulators (such as VIP or NPY-Y1R antagonists) via smart biomaterials, including stimuli-responsive hydrogels [281,282], offers a promising therapeutic approach. By directly remodeling the local microenvironment, this method prevents the off-target effects of systemic delivery, such as unintended bone loss. During fracture repair, this intervention enhances callus stability while maintaining systemic homeostasis. In degenerated discs, it interrupts the inflammatory cascade driven by abnormal sympathetic ingrowth, inhibits apoptosis, and reverses ECM degradation to drive structural repair.

However, clinical translation of this approach faces two primary challenges. First, the hostile intradiscal environment, including hypoxia, acidity, and elevated mechanical stress, restricts the prolonged release of these therapeutic agents [283-285]. Second, the high spatiotemporal heterogeneity of neural signaling during fracture healing complicates the precise control of the therapeutic window [286]. Future research should develop spatiotemporally controlled delivery systems that respond to local microenvironmental changes for on-demand drug release. Advances in precision medicine are expected to facilitate the development of personalized neuroregulatory therapies and promote multidisciplinary collaboration, thereby accelerating the clinical translation of nervous system-based treatments for bone diseases.

Although the role of the ANS in bone metabolism has garnered significant attention, several key challenges hinder the integration of mechanistic understanding and its clinical translation. First, accumulating evidence indicates that ANS signaling is highly context-dependent. Biological responses can vary considerably based on factors such as receptor subtype (e.g., β_2 -AR/ β_3 -AR, D1/D2), ligand concentration, stimulation duration, or the pathological state of the cells. For example, activation of ARs suppresses both osteoclastogenesis and osteogenic differentiation of MSCs [82,114], while the effects of ACh are concentration-dependent [287,288]. Additionally, neurotransmitter interactions *in vivo*, influenced by receptor subtypes and the local microenvironment, further complicate interpretation and often lead to inconsistent results. Second, the translation of animal findings into clinically actionable strategies remains limited. Significant physiological differences between animals and humans raise concerns regarding the direct applicability of preclinical results [289]. Importantly, ANS modulation is inherently systemic, and prolonged pharmacological or neuromodulatory interventions may influence cardiovascular and metabolic functions [290,291]. Third, disease-specific neural signatures have been proposed, with sympathetic overactivity being associated with low body weight, reduced bone mass, and abnormal bone metabolism in AIS [260], as well as with metabolic alterations in OP [187,188] and breast cancer bone metastases [277]. Reliable screening markers, such as receptor expression levels or sensitivity indicators, remain unavailable, contributing to substantial inter-individual variability in clinical outcomes.

Therefore, future studies should clarify the subtype-specific mechanisms of different autonomic branches and establish reliable biomarkers to accurately assess neural status, which will be essential for the precise clinical translation of neuromodulatory strategies.

Abbreviations

2-AG: 2-Arachidonoylglycerol
 α -ARs: Alpha-adrenergic receptors
 β -ARs: Beta-adrenergic receptors
ACh: Acetylcholine
Adrb2: Adrenergic receptor beta 2
AIS: Adolescent idiopathic scoliosis
Akt: Protein kinase B
ALP: Alkaline phosphatase
ANS: Autonomic nervous system
AP-1: Activator protein 1
ARs: Adrenergic receptors
ATF4: Activating transcription factor 4
BHSCs: Bone marrow hematopoietic stem cells
BMAT: Bone marrow adipose tissue
BMD: Bone mineral density
BMI: Body mass index
BMSCs: Bone marrow-derived mesenchymal stem cells
cAMP: Cyclic adenosine monophosphate
CB1: Cannabinoid receptor type 1
CB2: Cannabinoid receptor type 2
CIN: Chromosomal instability
CNS: Central nervous system
CTX: C-terminal telopeptide of type I collagen
DA: Dopamine
D1R: Dopamine receptor D1
ECM: Extracellular matrix
ECS: Endocannabinoid system
ERK: Extracellular signal-regulated kinase
ES: Ewing sarcoma
GPCR: G protein-coupled receptor
HSCs: Hematopoietic stem cells
HSPCs: Hematopoietic stem and progenitor cells
IL: Interleukin
IVDD: Intervertebral disc degeneration
M3R: Muscarinic acetylcholine receptor M3
mAChRs: Muscarinic acetylcholine receptors
MMP: Matrix metalloproteinase
MSCs: Mesenchymal stem cells
nAChRs: Nicotinic acetylcholine receptors
NE: Norepinephrine
NFATc1: Nuclear factor of activated T cells cytoplasmic 1
NPCs: Nucleus pulposus cells
NPY: Neuropeptide Y
NPY2R: Neuropeptide Y receptor Y2
OA: Osteoarthritis
OCN: Osteocalcin
OP: Osteoporosis
OPG: Osteoprotegerin
OPN: Osteopontin
Pcd4: Programmed cell death 4
PKA: Protein kinase A
PSNS: Parasympathetic nervous system
PTH: Parathyroid hormone
RA: Rheumatoid arthritis
RANKL: Receptor activator of nuclear factor kappa-B ligand
ROS: Reactive oxygen species
SNRI: Serotonin and norepinephrine reuptake inhibitor
SNS: Sympathetic nervous system
SOX9: SRY-related HMG-box transcription factor 9

SYM: Sympathectomy
 TBI: Traumatic brain injury
 TNF: Tumor necrosis factor
 TRAP: Tartrate-resistant acid phosphatase
 tVNS: Transcutaneous auricular vagus nerve stimulation
 VIP: Vasoactive intestinal peptide
 VNS: Vagus nerve stimulation
 VPAC: Vasoactive intestinal peptide receptor

Acknowledgments

The authors sincerely appreciate the valuable insights provided by the National Clinical Research Center for Geriatric Disorders at Xiangya Hospital, Central South University, which contributed to discussions pertinent to this study. We also thank Springer Nature Author Services for assistance with English language editing.

Authors' contributions

YSL and WFX conceived the study and revised the manuscript. WJH and YKH drafted the manuscript and contributed to the viewpoint discussions. HZL, WHL, GY, and BZJ assisted with figure preparation and revision discussions. All authors read and approved the final manuscript.

Funding

This work was supported by the National Key R&D Program of China (2023YFC3603400), the National Natural Science Foundation of China (82472522, 92268115), the Projects of International Cooperation and Exchanges NSFC (W2421123), and the Hunan Provincial Science Fund for Distinguished Young Scholars (S2024JJJCQN0405).

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Orthopedics, Xiangya Hospital, Central South University, Changsha 410008, China. ²National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, China. ³Xiangya School of Medicine Central South University, Changsha 410083, China.

References

- Chen S, He T, Zhong Y, Chen M, Yao Q, Chen D, *et al.* Roles of focal adhesion proteins in skeleton and diseases. *Acta pharmaceutica Sinica B*. 2023;13(3):998-1013. <https://doi.org/10.1016/j.japsb.2022.09.020>.
- Li Z, Shi B, Li N, Sun J, Zeng X, Huang R, *et al.* Bone controls browning of white adipose tissue and protects from diet-induced obesity through Schnurri-3-regulated SLIT2 secretion. *Nat*

- Commun*. 2024;15(1):6697. <https://doi.org/10.1038/s41467-024-51155-6>.
- Li J, Zhang Z, Tang J, Hou Z, Li L, Li B. Emerging roles of nerve-bone axis in modulating skeletal system. *Med Res Rev*. 2024; 44(4):1867-903. <https://doi.org/10.1002/med.22031>.
- Xiao L, Zhu M, Yu K, Zhang Q, Dai Z, Weir MD, *et al.* Effects of innervation on angiogenesis and osteogenesis in bone and dental tissue engineering. *Tissue Eng Part B Rev*. 2024;30(4):477-89. <https://doi.org/10.1089/ten.TEB.2023.0267>.
- Ma C, Zhang Y, Cao Y, Hu CH, Zheng CX, Jin Y, *et al.* Autonomic neural regulation in mediating the brain-bone axis: mechanisms and implications for regeneration under psychological stress. *QJM*. 2024;117(2):95-108. <https://doi.org/10.1093/qjmed/hcad108>.
- Lv X, Gao F, Li TP, Xue P, Wang X, Wan M, *et al.* Skeleton interoception regulates bone and fat metabolism through hypothalamic neuroendocrine NPY. *Elife*. 2021;10(10):e70324. <https://doi.org/10.7554/eLife.70324>.
- Wan QQ, Qin WP, Ma YX, Shen MJ, Li J, Zhang ZB, *et al.* Crosstalk between bone and nerves within bone. *Adv Sci*. 2021;8(7): 2003390. <https://doi.org/10.1002/adv.202003390>.
- Eleftheriou F. Impact of the autonomic nervous system on the skeleton. *Physiol Rev*. 2018;98(3):1083-112. <https://doi.org/10.1152/physrev.00014.2017>.
- Jenei-Lanzl Z, Straub RH. β 2-adrenoceptors kick osteoarthritis – time to rethink prevention and therapy. *Osteoarthr Cartilage*. 2024;32(12):1522-9. <https://doi.org/10.1016/j.joca.2024.06.012>.
- Courties A, Sellam J, Berenbaum F. Role of the autonomic nervous system in osteoarthritis. *Best Pract Res Clin Rheumatol*. 2017;31(5):661-75. <https://doi.org/10.1016/j.berh.2018.04.001>.
- Zhou L, Kwok CK, Ran D, Ashbeck EL, Lo-Ciganic WH. Lack of evidence that beta blocker use reduces knee pain, areas of joint pain, or analgesic use among individuals with symptomatic knee osteoarthritis. *Osteoarthr Cartilage*. 2020;28(1):53-61. <https://doi.org/10.1016/j.joca.2019.08.008>.
- Sun K, Sun J, Yan C, Sun J, Xu X, Shi J. Sympathetic neurotransmitter, VIP, delays intervertebral disc degeneration via FGF18/FGFR2-mediated activation of Akt signaling pathway. *Adv Biol (Weinh)*. 2024;8(3):e2300250. <https://doi.org/10.1002/adbi.202300250>.
- Hu B, Lv X, Chen H, Xue P, Gao B, Wang X, *et al.* Sensory nerves regulate mesenchymal stromal cell lineage commitment by tuning sympathetic tones. *J Clin Invest*. 2020;130(7):3483-98. <https://doi.org/10.1172/JCI131554>.
- Alves Barreto AE, Balera Brito VG, Patrocinio MS, Ballasconi BB, Tfaile Frasnelli SC, Penha Oliveira SH. Beta1-adrenergic receptor but not beta2 mediates osteogenic differentiation of bone marrow mesenchymal stem cells in normotensive and hypertensive rats. *Eur J Pharmacol*. 2021;911(911):174515. <https://doi.org/10.1016/j.ejphar.2021.174515>.
- Xie W, Li F, Han Y, Qin Y, Wang Y, Chi X, *et al.* Neuropeptide Y1 receptor antagonist promotes osteoporosis and microdamage repair and enhances osteogenic differentiation of bone marrow stem cells via cAMP/PKA/CREB pathway. *Aging*. 2020;12(9):8120-36. <https://doi.org/10.18632/aging.103129>.
- Wang L, Han L, Xue P, Hu X, Wong SW, Deng M, *et al.* Dopamine suppresses osteoclast differentiation via cAMP/PKA/CREB pathway. *Cell Signal*. 2021;78(78):109847. <https://doi.org/10.1016/j.cellsig.2020.109847>.
- Yao Q, Liang H, Huang B, Xiang L, Wang T, Xiong Y, *et al.* Beta-

- adrenergic signaling affect osteoclastogenesis via osteocytic MLO-Y4 cells' RANKL production. *Biochem Biophys Res Commun*. 2017;488(4):634-40. <https://doi.org/10.1016/j.bbrc.2016.11.011>.
18. Lorenz J, Schafer N, Bauer R, Jenei-Lanzl Z, Springorum RH, Grassel S. Norepinephrine modulates osteoarthritic chondrocyte metabolism and inflammatory responses. *Osteoarthr Cartilage*. 2016;24(2):325-34. <https://doi.org/10.1016/j.joca.2015.08.007>.
19. Li F, Xie W, Chen Z, Zhou Z, Wang Z, Xiao J, et al. Neuropeptide Y and receptors are associated with the pyroptosis of nucleus pulposus in aging and degenerative intervertebral discs of rats. *Neuropeptides*. 2022;96(96):102284. <https://doi.org/10.1016/j.npep.2022.102284>.
20. Sun K, Zhu J, Sun J, Sun X, Huan L, Zhang B, et al. Neuropeptide Y prevents nucleus pulposus cells from cell apoptosis and IL-1beta-induced extracellular matrix degradation. *Cell Cycle*. 2021;20(10):960-77. <https://doi.org/10.1080/15384101.2021.1911914>.
21. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. *Nature*. 2014;505(7483):327-34. <https://doi.org/10.1038/nature12984>.
22. Spieker J, Friess JL, Sperling L, Thangaraj G, Vogel-Hopker A, Layer PG. Cholinergic control of bone development and beyond. *Int Immunopharmacol*. 2020;83(83):106405. <https://doi.org/10.1016/j.intimp.2020.106405>.
23. Tracey KJ. Physiology and immunology of the cholinergic anti-inflammatory pathway. *J Clin Invest*. 2007;117(2):289-96. <https://doi.org/10.1172/JCI30555>.
24. Wehrwein EA, Orer HS, Barman SM. Overview of the anatomy, physiology, and pharmacology of the autonomic nervous system. *Compr Physiol*. 2016;6(3):1239-78. <https://doi.org/10.1002/cphy.c150037>.
25. Sisask G, Silfversward CJ, Bjurholm A, Nilsson O. Ontogeny of sensory and autonomic nerves in the developing mouse skeleton. *Auton Neurosci*. 2013;177(2):237-43. <https://doi.org/10.1016/j.autneu.2013.05.005>.
26. Tai MDS, Gamiz-Arco G, Martinez A. Dopamine synthesis and transport: current and novel therapeutics for parkinsonisms. *Biochem Soc Trans*. 2024;52(3):1275-91. <https://doi.org/10.1042/BST20231061>.
27. Lou JS, Su M, Wang J, Do HN, Miao Y, Huang XY. Distinct binding conformations of epinephrine with alpha- and beta-adrenergic receptors. *Exp Mol Med*. 2024;56(9):1952-66. <https://doi.org/10.1038/s12276-024-01296-x>.
28. Wu Y, Zeng L, Zhao S. Ligands of adrenergic receptors: a structural point of view. *Biomolecules*. 2021;11(7):936. <https://doi.org/10.3390/biom11070936>.
29. Zhao Y, Peng X, Wang Q, Zhang Z, Wang L, Xu Y, et al. Crosstalk between the neuroendocrine system and bone homeostasis. *Endocr Rev*. 2024;45(1):95-124. <https://doi.org/10.1210/endo/bnad025>.
30. Ham D, Inoue A, Xu J, Du Y, Chung KY. Molecular mechanism of muscarinic acetylcholine receptor M3 interaction with Gq. *Commun Biol*. 2024;7(1):362. <https://doi.org/10.1038/s42003-024-06056-1>.
31. Kang X, Qian Z, Liu J, Feng D, Li H, Zhang Z, et al. Neuropeptide Y acts directly on cartilage homeostasis and exacerbates progression of osteoarthritis through NPY2R. *J Bone Miner Res*. 2020;35(7):1375-84. <https://doi.org/10.1002/jbmr.3991>.
32. Assefa F. The role of sensory and sympathetic nerves in craniofacial bone regeneration. *Neuropeptides*. 2023;99(99):102328. <https://doi.org/10.1016/j.npep.2023.102328>.
33. Lee NJ, Nguyen AD, Enriquez RF, Doyle KL, Sainsbury A, Baldock PA, et al. Osteoblast specific Y1 receptor deletion enhances bone mass. *Bone*. 2011;48(3):461-7. <https://doi.org/10.1016/j.bone.2010.10.174>.
34. Zhang Y, Chen CY, Liu YW, Rao SS, Tan YJ, Qian YX, et al. Neuronal induction of bone-fat imbalance through osteocyte neuropeptide Y. *Adv Sci (Weinh)*. 2021;8(24):e2100808. <https://doi.org/10.1002/advs.202100808>.
35. Shi YC, Lin S, Wong IP, Baldock PA, Aljanova A, Enriquez RF, et al. NPY neuron-specific Y2 receptors regulate adipose tissue and trabecular bone but not cortical bone homeostasis in mice. *PLoS One*. 2010;5(6):e11361. <https://doi.org/10.1371/journal.pone.0011361>.
36. Seldeen KL, Halley PG, Volmar CH, Rodriguez MA, Hernandez M, Pang M, et al. Neuropeptide Y Y2 antagonist treated ovariectomized mice exhibit greater bone mineral density. *Neuropeptides*. 2018;67:45-55. <https://doi.org/10.1016/j.npep.2017.11.005>.
37. Chen QC, Zhang Y. The role of NPY in the regulation of bone metabolism. *Front Endocrinol (Lausanne)*. 2022;13:833485. <https://doi.org/10.3389/fendo.2022.833485>.
38. Allison SJ, Baldock P, Sainsbury A, Enriquez R, Lee NJ, Lin EJ, et al. Conditional deletion of hypothalamic Y2 receptors reverts gonadectomy-induced bone loss in adult mice. *J Biol Chem*. 2006;281(33):23436-44. <https://doi.org/10.1074/jbc.M604839200>.
39. Hohmann EL, Elde RP, Rysavy JA, Einzig S, Gebhard RL. Innervation of periosteum and bone by sympathetic vasoactive intestinal peptide-containing nerve fibers. *Science*. 1986;232(4752):868-71. <https://doi.org/10.1126/science.3518059>.
40. Shi L, Liu Y, Yang Z, Wu T, Lo HT, Xu J, et al. Vasoactive intestinal peptide promotes fracture healing in sympathectomized mice. *Calcif Tissue Int*. 2021;109(1):55-65. <https://doi.org/10.1007/s00223-021-00820-9>.
41. Castro-Vazquez D, Arribas-Castano P, Garcia-Lopez I, Gutierrez-Canas I, Perez-Garcia S, Lamana A, et al. Vasoactive intestinal peptide exerts an osteoinductive effect in human mesenchymal stem cells. *Biofactors*. 2024;50(6):1148-60. <https://doi.org/10.1002/biof.2062>.
42. Lu J, Piper SJ, Zhao P, Miller LJ, Wootten D, Sexton PM. Targeting VIP and PACAP receptor signaling: new insights into designing drugs for the PACAP subfamily of receptors. *Int J Mol Sci*. 2022;23(15):8069. <https://doi.org/10.3390/ijms23158069>.
43. Beaudeau D, Schwenn P, McLoughlin LT, Parker M, Boyes A, Simcock G, et al. A novel, complex systems approach to modelling risk of psychological distress in young adolescents. *Sci Rep*. 2021;11(1):9428. <https://doi.org/10.1038/s41598-021-88932-y>.
44. Lundberg P, Lundgren I, Mukohyama H, Lehenkari PP, Horton MA, Lerner UH. Vasoactive intestinal peptide (VIP)/pituitary adenylate cyclase-activating peptide receptor subtypes in mouse calvarial osteoblasts: presence of VIP-2 receptors and differentiation-induced expression of VIP-1 receptors. *Endocrinology*. 2001;142(1):339-47. <https://doi.org/10.1210/endo.142.1.7912>.
45. Castro-Vazquez D, Lamana A, Arribas-Castano P, Gutierrez-Canas I, Villanueva-Romero R, Perez-Garcia S, et al. The neuropeptide VIP limits human osteoclastogenesis: clinical associations with bone metabolism markers in patients with early arthritis. *Biomedicines*. 2021;9(12):1880. <https://doi.org/10.3390/biomedicines9121880>.
46. Bliziotis M, McLoughlin S, Gunness M, Fumagalli F, Jones SR, Caron MG. Bone histomorphometric and biomechanical

- abnormalities in mice homozygous for deletion of the dopamine transporter gene. *Bone*. 2000;26(1):15-9. [https://doi.org/10.1016/s8756-3282\(99\)00232-x](https://doi.org/10.1016/s8756-3282(99)00232-x).
47. Tsai KY, Lee CC, Chou YM, Shen SP, Su CY, Wu HC, et al. The risks of major osteoporotic fractures in patients with schizophrenia: a population-based 10-year follow-up study. *Schizophr Res*. 2014;159(2-3):322-8. <https://doi.org/10.1016/j.schres.2014.09.032>.
48. Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011; 63(1):182-217. <https://doi.org/10.1124/pr.110.002642>.
49. Liu T, Wu H, Li J, Zhu C, Wei J. Unraveling the bone-brain axis: a new frontier in Parkinson's disease research. *Int J Mol Sci*. 2024; 25(23):12842. <https://doi.org/10.3390/ijms252312842>.
50. Lima DP, Chagas-Neto FAD, Gomes de Luna JR, Martins YO, de Almeida SB, Feitosa CX, et al. Osteoporosis in Parkinson's disease and the role of lean body mass: a cross-sectional study in a Brazilian tertiary center. *Front Endocrinol (Lausanne)*. 2024; 15:1326212. <https://doi.org/10.3389/fendo.2024.1326212>.
51. Kuang Z, Chen Z, Tu S, Mai Z, Chen L, Kang X, et al. Dopamine suppresses osteogenic differentiation of rat bone marrow-derived mesenchymal stem cells via Akt/GSK-3 β /beta-catenin signaling pathway. *Stem Cells Int*. 2022;2022:4154440. <https://doi.org/10.1155/2022/4154440>.
52. Sun H, Feng Y, Tu S, Zhou J, Wang Y, Wei J, et al. Dopamine promotes osteogenic differentiation of PDLSCs by activating DRD1 and DRD2 during orthodontic tooth movement via ERK1/2 signaling pathway. *Regen Ther*. 2024;27:268-78. <https://doi.org/10.1016/j.reth.2024.03.025>.
53. Stefanakis K, Upadhyay J, Ramirez-Cisneros A, Patel N, Sahai A, Mantzoros CS. Leptin physiology and pathophysiology in energy homeostasis, immune function, neuroendocrine regulation and bone health. *Metabolism*. 2024;161:156056. <https://doi.org/10.1016/j.metabol.2024.156056>.
54. Pereira S, Cline DL, Glavas MM, Covey SD, Kieffer TJ. Tissue-specific effects of leptin on glucose and lipid metabolism. *Endocr Rev*. 2021;42(1):1-28. <https://doi.org/10.1210/endrev/bnaa027>.
55. Reid IR, Baldock PA, Cornish J. Effects of leptin on the skeleton. *Endocr Rev*. 2018;39(6):938-59. <https://doi.org/10.1210/er.2017-00226>.
56. Zhou BO, Yue R, Murphy MM, Peyer JG, Morrison SJ. Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow. *Cell Stem Cell*. 2014;15(2):154-68. <https://doi.org/10.1016/j.stem.2014.06.008>.
57. Takeda S, Eleftheriou F, Levasseur R, Liu X, Zhao L, Parker KL, et al. Leptin regulates bone formation via the sympathetic nervous system. *Cell*. 2002;111(3):305-17. [https://doi.org/10.1016/s0092-8674\(02\)01049-8](https://doi.org/10.1016/s0092-8674(02)01049-8).
58. Eleftheriou F, Takeda S, Ebihara K, Magre J, Patano N, Kim CA, et al. Serum leptin level is a regulator of bone mass. *Proc Natl Acad Sci U S A*. 2004;101(9):3258-63. <https://doi.org/10.1073/pnas.0308744101>.
59. Karsenty G. Convergence between bone and energy homeostases: leptin regulation of bone mass. *Cell Metab*. 2006; 4(5):341-8. <https://doi.org/10.1016/j.cmet.2006.10.008>.
60. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, et al. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. *Cell*. 2000;100(2):197-207. [https://doi.org/10.1016/s0092-8674\(00\)81558-5](https://doi.org/10.1016/s0092-8674(00)81558-5).
61. Holloway WR, Collier FM, Aitken CJ, Myers DE, Hodge JM, Malakellis M, et al. Leptin inhibits osteoclast generation. *J Bone Miner Res*. 2002;17(2):200-9. <https://doi.org/10.1359/jbmr.2002.17.2.200>.
62. Deis S, Srivastava RK, Ruiz de Azua I, Bindila L, Baraghithy S, Lutz B, et al. Age-related regulation of bone formation by the sympathetic cannabinoid CB1 receptor. *Bone*. 2018;108(108):34-42. <https://doi.org/10.1016/j.bone.2017.12.018>.
63. Serban M, Toader C, Covache-Busioc RA. The endocannabinoid system in human disease: molecular signaling, receptor pharmacology, and therapeutic innovation. *Int J Mol Sci*. 2025; 26(22):11132. <https://doi.org/10.3390/ijms262211132>.
64. Baraghithy S, Soae Y, Assaf D, Hinden L, Udi S, Drori A, et al. Renal proximal tubule cell cannabinoid-1 receptor regulates bone remodeling and mass via a kidney-to-bone axis. *Cells*. 2021;10(2): 414. <https://doi.org/10.3390/cells10020414>.
65. Apostu D, Lucaciu O, Mester A, Benea H, Oltean-Dan D, Onisor F, et al. Cannabinoids and bone regeneration. *Drug Metab Rev*. 2019;51(1):65-75. <https://doi.org/10.1080/03602532.2019.1574303>.
66. Idris AI, van 't Hof RJ, Greig IR, Ridge SA, Baker D, Ross RA, et al. Regulation of bone mass, bone loss and osteoclast activity by cannabinoid receptors. *Nat Med*. 2005;11(7):774-9. <https://doi.org/10.1038/nm1255>.
67. Bab I, Zimmer A, Melamed E. Cannabinoids and the skeleton: from marijuana to reversal of bone loss. *Ann Med*. 2009;41(8):560-7. <https://doi.org/10.1080/07853890903121025>.
68. Idris AI, Ralston SH. Role of cannabinoids in the regulation of bone remodeling. *Front Endocrinol (Lausanne)*. 2012;3(3):136. <https://doi.org/10.3389/fendo.2012.00136>.
69. Tam J, Trembovler V, Di Marzo V, Petrosino S, Leo G, Alexandrovich A, et al. The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. *FASEB J*. 2008;22(1):285-94. <https://doi.org/10.1096/fj.06-7957com>.
70. Al-Azab M, Safi M, Idiatullina E, Al-Shaebi F, Zaky MY. Aging of mesenchymal stem cell: machinery, markers, and strategies of fighting. *Cell Mol Biol Lett*. 2022;27(1):69. <https://doi.org/10.1186/s11658-022-00366-0>.
71. Jo H, Brito S, Kwak BM, Park S, Lee MG, Bin BH. Applications of mesenchymal stem cells in skin regeneration and rejuvenation. *Int J Mol Sci*. 2021;22(5):2410. <https://doi.org/10.3390/ijms22052410>.
72. Luo Y, Liu B, Qiu Y, Li L, Yang F, Zhang C, et al. Divalent metal ions enhance bone regeneration through modulation of nervous systems and metabolic pathways. *Bioact Mater*. 2025;47:432-47. <https://doi.org/10.1016/j.bioactmat.2025.01.034>.
73. Hedderich J, El Bagdadi K, Angele P, Grassel S, Meurer A, Straub RH, et al. Norepinephrine inhibits the proliferation of human bone marrow-derived mesenchymal stem cells via beta2-adrenoceptor-mediated ERK1/2 and PKA phosphorylation. *Int J Mol Sci*. 2020;21(11):3924. <https://doi.org/10.3390/ijms21113924>.
74. Kong Y, Cheng L, Ma L, Li H, Cheng B, Zhao Y. Norepinephrine protects against apoptosis of mesenchymal stem cells induced by high glucose. *J Cell Physiol*. 2019;234(11):20801-15. <https://doi.org/10.1002/jcp.28686>.
75. Wu Y, Zhang Q, Zhao B, Wang X. Effect and mechanism of propranolol on promoting osteogenic differentiation and early implant osseointegration. *Int J Mol Med*. 2021;48(4):191. <https://doi.org/10.3892/ijmm.2021.5024>.
76. Zablotni A, Dakischew O, Trinkaus K, Hartmann S, Szalay G, Heiss C,

- et al. Regulation of acetylcholine receptors during differentiation of bone mesenchymal stem cells harvested from human reaming debris. *Int Immunopharmacol*. 2015;29(1):119-26. <https://doi.org/10.1016/j.intimp.2015.07.021>.
77. Tang JM, Yuan J, Li Q, Wang JN, Kong X, Zheng F, et al. Acetylcholine induces mesenchymal stem cell migration via Ca^{2+} /PKC/ERK1/2 signal pathway. *J Cell Biochem*. 2012;113(8):2704-13. <https://doi.org/10.1002/jcb.24148>.
78. Schraufstatter IU, DiScipio RG, Khaldoyanidi SK. Alpha 7 subunit of nAChR regulates migration of human mesenchymal stem cells. *J Stem Cells*. 2009;4(4):203-15. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2925301/pdf/nihms205013.pdf>.
79. Oliveira CS, Carreira M, Correia CR, Mano JF. The therapeutic potential of hematopoietic stem cells in bone regeneration. *Tissue Eng Part B Rev*. 2022;28(2):379-92. <https://doi.org/10.1089/ten.TEB.2021.0019>.
80. Dong P, Gu X, Zhu G, Li M, Ma B, Zi Y. Melatonin induces osteoblastic differentiation of mesenchymal stem cells and promotes fracture healing in a rat model of femoral fracture via neuropeptide Y/neuropeptide Y receptor Y1 signaling. *Pharmacology*. 2018;102(5-6):272-80. <https://doi.org/10.1159/000492576>.
81. Wang CX, Ge XY, Wang MY, Ma T, Zhang Y, Lin Y. Dopamine D1 receptor-mediated activation of the ERK signaling pathway is involved in the osteogenic differentiation of bone mesenchymal stem cells. *Stem Cell Res Ther*. 2020;11(1):12. <https://doi.org/10.1186/s13287-019-1529-x>.
82. Du Z, Wang L, Zhao Y, Cao J, Wang T, Liu P, et al. Sympathetic denervation-induced MSC mobilization in distraction osteogenesis associates with inhibition of MSC migration and osteogenesis by norepinephrine/adrb3. *PLoS One*. 2014;9(8):e105976. <https://doi.org/10.1371/journal.pone.0105976>.
83. Shi L, Feng L, Zhu ML, Yang ZM, Wu TY, Xu J, et al. Vasoactive intestinal peptide stimulates bone marrow-mesenchymal stem cells osteogenesis differentiation by activating Wnt/beta-catenin signaling pathway and promotes rat skull defect repair. *Stem Cells Dev*. 2020;29(10):655-66. <https://doi.org/10.1089/scd.2019.0148>.
84. Intemann J, De Gorter DJJ, Naylor AJ, Dankbar B, Wehmeyer C. Importance of osteocyte-mediated regulation of bone remodelling in inflammatory bone disease. *Swiss Med Wkly*. 2020;150:w20187. <https://doi.org/10.4414/smw.2020.20187>.
85. Dalle Carbonare L, Cominacini M, Trabetti E, Bombieri C, Pessoa J, Romanelli MG, et al. The bone microenvironment: new insights into the role of stem cells and cell communication in bone regeneration. *Stem Cell Res Ther*. 2025;16(1):169. <https://doi.org/10.1186/s13287-025-04288-4>.
86. Erndt-Marino JD, Hahn MS. Probing the response of human osteoblasts following exposure to sympathetic neuron-like PC-12 cells in a 3D coculture model. *J Biomed Mater Res A*. 2017;105(4):984-90. <https://doi.org/10.1002/jbm.a.35964>.
87. Horsnell H, Baldock PA. Osteoblastic actions of the neuropeptide Y system to regulate bone and energy homeostasis. *Curr Osteoporos Rep*. 2016;14(1):26-31. <https://doi.org/10.1007/s11914-016-0300-9>.
88. Huang J, Wu T, Jiang YR, Zheng XQ, Wang H, Liu H, et al. Beta-receptor blocker enhances the anabolic effect of PTH after osteoporotic fracture. *Bone Res*. 2024;12(1):18. <https://doi.org/10.1038/s41413-024-00321-z>.
89. Hu CH, Sui BD, Liu J, Dang L, Chen J, Zheng CX, et al. Sympathetic neurostress drives osteoblastic exosomal miR-21 transfer to disrupt bone homeostasis and promote osteopenia. *Small Methods*. 2022;6(3):e2100763. <https://doi.org/10.1002/smt.202100763>.
90. Kondo A, Togari A. *In vivo* stimulation of sympathetic nervous system modulates osteoblastic activity in mouse calvaria. *Am J Physiol Endocrinol Metab*. 2003;285(3):E661-7. <https://doi.org/10.1152/ajpendo.00026.2003>.
91. Kwan Tat S, Padrines M, Theoleyre S, Heymann D, Fortun Y. IL-6, RANKL, TNF-alpha/IL-1: interrelations in bone resorption pathophysiology. *Cytokine Growth Factor Rev*. 2004;15(1):49-60. <https://doi.org/10.1016/j.cytogfr.2003.10.005>.
92. Nakagawa M, Kaneda T, Arakawa T, Morita S, Sato T, Yomada T, et al. Vascular endothelial growth factor (VEGF) directly enhances osteoclastic bone resorption and survival of mature osteoclasts. *FEBS Lett*. 2000;473(2):161-4. [https://doi.org/10.1016/S0014-5793\(00\)01520-9](https://doi.org/10.1016/S0014-5793(00)01520-9).
93. Sato T, Abe T, Chida D, Nakamoto N, Hori N, Kokabu S, et al. Functional role of acetylcholine and the expression of cholinergic receptors and components in osteoblasts. *FEBS Lett*. 2010;584(4):817-24. <https://doi.org/10.1016/j.febslet.2010.01.001>.
94. Gadowski S, Fielding C, Garcia-Garcia A, Korn C, Kapeni C, Ashraf S, et al. A cholinergic neuroskeletal interface promotes bone formation during postnatal growth and exercise. *Cell Stem Cell*. 2022;29(4):528-44.e9. <https://doi.org/10.1016/j.stem.2022.02.008>.
95. Fonseca TL, Jorgetti V, Costa CC, Capelo LP, Covarrubias AE, Moulatlet AC, et al. Double disruption of alpha2A- and alpha2C-adrenoceptors results in sympathetic hyperactivity and high-bone-mass phenotype. *J Bone Miner Res*. 2011;26(3):591-603. <https://doi.org/10.1002/jbmr.243>.
96. Kajimura D, Hinoi E, Ferron M, Kode A, Riley KJ, Zhou B, et al. Genetic determination of the cellular basis of the sympathetic regulation of bone mass accrual. *J Exp Med*. 2011;208(4):841-51. <https://doi.org/10.1084/jem.20102608>.
97. Tanaka K, Hirai T, Kodama D, Kondo H, Hamamura K, Togari A. $\alpha 1B$ -adrenoceptor signalling regulates bone formation through the up-regulation of CCAAT/enhancer-binding protein delta expression in osteoblasts. *Br J Pharmacol*. 2016;173(6):1058-69. <https://doi.org/10.1111/bph.13418>.
98. Shi Y, Oury F, Yadav VK, Wess J, Liu XS, Guo XE, et al. Signaling through the M3 muscarinic receptor favors bone mass accrual by decreasing sympathetic activity. *Cell Metab*. 2010;11(3):231-8. <https://doi.org/10.1016/j.cmet.2010.01.005>.
99. Bajayo A, Bar A, Denes A, Bachar M, Kram V, Attar-Namdar M, et al. Skeletal parasympathetic innervation communicates central IL-1 signals regulating bone mass accrual. *Proc Natl Acad Sci U S A*. 2012;109(38):15455-60. <https://doi.org/10.1073/pnas.1206061109>.
100. Fu L, Patel MS, Bradley A, Wagner EF, Karsenty G. The molecular clock mediates leptin-regulated bone formation. *Cell*. 2005;122(5):803-15. <https://doi.org/10.1016/j.cell.2005.06.028>.
101. Kodama D, Togari A. Noradrenaline stimulates cell proliferation by suppressing potassium channels via Gi/o-protein-coupled $\alpha 1B$ -adrenoceptors in human osteoblasts. *Br J Pharmacol*. 2013;168(5):1230-9. <https://doi.org/10.1111/bph.12000>.
102. Sato T, Abe T, Nakamoto N, Tomaru Y, Koshikiya N, Nojima J, et al. Nicotine induces cell proliferation in association with cyclin D1 up-regulation and inhibits cell differentiation in association with p53 regulation in a murine pre-osteoblastic cell line. *Biochem Biophys Res Commun*. 2008;377(1):126-30. <https://doi.org/10.1016/j.bbrc.2008.09.114>.

103. Liu PS, Chen YY, Feng CK, Lin YH, Yu TC. Muscarinic acetylcholine receptors present in human osteoblast and bone tissue. *Eur J Pharmacol.* 2011;650(1):34-40. <https://doi.org/10.1016/j.ejphar.2010.09.031>.
104. Baldock PA, Lin S, Zhang L, Karl T, Shi Y, Driessler F, et al. Neuropeptide Y attenuates stress-induced bone loss through suppression of noradrenaline circuits. *J Bone Miner Res.* 2014; 29(10):2238-49. <https://doi.org/10.1002/jbmr.2205>.
105. Liu X, Liu H, Xiong Y, Yang L, Wang C, Zhang R, et al. Postmenopausal osteoporosis is associated with the regulation of SP, CGRP, VIP, and NPY. *Biomed Pharmacother.* 2018;104(104):742-50. <https://doi.org/10.1016/j.biopha.2018.04.044>.
106. Zhu J, Feng C, Zhang W, Wang Z, Zhong M, Tang W, et al. Activation of dopamine receptor D1 promotes osteogenic differentiation and reduces glucocorticoid-induced bone loss by upregulating the ERK1/2 signaling pathway. *Mol Med.* 2022;28(1):23. <https://doi.org/10.1186/s10020-022-00453-0>.
107. Doherty AH, Ghalambor CK, Donahue SW. Evolutionary physiology of bone: bone metabolism in changing environments. *Physiology (Bethesda).* 2015;30(1):17-29. <https://doi.org/10.1152/physiol.00022.2014>.
108. Rodrigues WF, Madeira MF, da Silva TA, Clemente-Napimoga JT, Miguel CB, Dias-da-Silva VJ, et al. Low dose of propranolol down-modulates bone resorption by inhibiting inflammation and osteoclast differentiation. *Br J Pharmacol.* 2012;165(7):2140-51. <https://doi.org/10.1111/j.1476-5381.2011.01686.x>.
109. Sui B, Liu J, Zheng C, Dang L, Chen J, Cao Y, et al. Targeted inhibition of osteoclastogenesis reveals the pathogenesis and therapeutics of bone loss under sympathetic neurostress. *Int J Oral Sci.* 2022;14(1):39. <https://doi.org/10.1038/s41368-022-00193-1>.
110. Kondo H, Takeuchi S, Togari A. beta-Adrenergic signaling stimulates osteoclastogenesis via reactive oxygen species. *Am J Physiol Endocrinol Metab.* 2013;304(5):E507-15. <https://doi.org/10.1152/ajpendo.00191.2012>.
111. Zhao W, Li J, Su T, Wang C, Fu Y, Li C, et al. Osteoclast activation and inflammatory bone diseases: focusing on receptors in osteoclasts. *J Inflamm Res.* 2025;18:3201-13. <https://doi.org/10.2147/JIR.S507269>.
112. Yang S, He Z, Wu T, Wang S, Dai H. Glycobiology in osteoclast differentiation and function. *Bone Res.* 2023;11(1):55. <https://doi.org/10.1038/s41413-023-00293-6>.
113. de Molon RS, Vernal R, Oliveira GE, Steffens JP, Ervolino E, Theodoro LH, et al. Inflammatory bone loss and signaling pathways in periodontitis: mechanistic insights and emerging therapeutic strategies. *Bone Res.* 2026;14(1):1. <https://doi.org/10.1038/s41413-025-00478-1>.
114. Hamajima K, Hamamura K, Chen A, Yokota H, Mori H, Yo S, et al. Suppression of osteoclastogenesis via alpha2-adrenergic receptors. *Biomed Rep.* 2018;8(5):407-16. <https://doi.org/10.3892/br.2018.1075>.
115. Eleftheriou F, Ahn JD, Takeda S, Starbuck M, Yang X, Liu X, et al. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature.* 2005;434(7032):514-20. <https://doi.org/10.1038/nature03398>.
116. Teitelbaum SL, Ross FP. Genetic regulation of osteoclast development and function. *Nat Rev Genet.* 2003;4(8):638-49. <https://doi.org/10.1038/nrg1122>.
117. Mandl P, Hayer S, Karonitsch T, Scholze P, Gyori D, Sykourti D, et al. Nicotinic acetylcholine receptors modulate osteoclastogenesis. *Arthritis Res Ther.* 2016;18(18):63. <https://doi.org/10.1186/s13075-016-0961-x>.
118. Sun S, Diggins NH, Gunderson ZJ, Fehrenbacher JC, White FA, Kacena MA. No pain, no gain? The effects of pain-promoting neuropeptides and neurotrophins on fracture healing. *Bone.* 2020;131(131):115109. <https://doi.org/10.1016/j.bone.2019.115109>.
119. Qu H, Zhuang Y, Zhu L, Zhao Z, Wang K. The effects of vasoactive intestinal peptide on RANKL-induced osteoclast formation. *Ann Transl Med.* 2021;9(2):127. <https://doi.org/10.21037/atm-20-7607>.
120. Yang H, Xu Y, Zhu M, Gu Y, Zhang W, Shao H, et al. Inhibition of titanium-particle-induced inflammatory osteolysis after local administration of dopamine and suppression of osteoclastogenesis via D2-like receptor signaling pathway. *Biomaterials.* 2016;80(80):1-10. <https://doi.org/10.1016/j.biomaterials.2015.11.046>.
121. Geng D, Xu Y, Yang H, Wang J, Zhu X, Zhu G, et al. Protection against titanium particle induced osteolysis by cannabinoid receptor 2 selective antagonist. *Biomaterials.* 2010;31(8):1996-2000. <https://doi.org/10.1016/j.biomaterials.2009.11.069>.
122. Hanami K, Nakano K, Saito K, Okada Y, Yamaoka K, Kubo S, et al. Dopamine D2-like receptor signaling suppresses human osteoclastogenesis. *Bone.* 2013;56(1):1-8. <https://doi.org/10.1016/j.bone.2013.04.019>.
123. Amano S, Arai M, Goto S, Togari A. Inhibitory effect of NPY on isoprenaline-induced osteoclastogenesis in mouse bone marrow cells. *Biochim Biophys Acta.* 2007;1770(6):966-73. <https://doi.org/10.1016/j.bbagen.2007.02.009>.
124. Aitken SJ, Landao-Bassonga E, Ralston SH, Idris AI. Beta2-adrenoreceptor ligands regulate osteoclast differentiation *in vitro* by direct and indirect mechanisms. *Arch Biochem Biophys.* 2009;482(1-2):96-103. <https://doi.org/10.1016/j.abb.2008.11.012>.
125. Igwe JC, Jiang X, Paic F, Ma L, Adams DJ, Baldock PA, et al. Neuropeptide Y is expressed by osteocytes and can inhibit osteoblastic activity. *J Cell Biochem.* 2009;108(3):621-30. <https://doi.org/10.1002/jcb.22294>.
126. Wu KC, Chang YH, Ding DC, Lin SZ. Mesenchymal stromal cells for aging cartilage regeneration: a review. *Int J Mol Sci.* 2024; 25(23):12911. <https://doi.org/10.3390/ijms252312911>.
127. Lee MS, Lin EC, Sivapatham A, Leiferman EM, Jiao H, Lu Y, et al. Autologous iPSC- and MSC-derived chondrocyte implants for cartilage repair in a miniature pig model. *Stem Cell Res Ther.* 2025;16(1):86. <https://doi.org/10.1186/s13287-025-04215-7>.
128. Hall AC. The role of chondrocyte morphology and volume in controlling phenotype-implications for osteoarthritis, cartilage repair, and cartilage engineering. *Curr Rheumatol Rep.* 2019;21(8):38. <https://doi.org/10.1007/s11926-019-0837-6>.
129. Bacenkova D, Trebunova M, Demeterova J, Zivcak J. Human chondrocytes, metabolism of articular cartilage, and strategies for application to tissue engineering. *Int J Mol Sci.* 2023;24(23):17096. <https://doi.org/10.3390/ijms242317096>.
130. Grassel S, Muschter D. Peripheral nerve fibers and their neurotransmitters in osteoarthritis pathology. *Int J Mol Sci.* 2017; 18(5):931. <https://doi.org/10.3390/ijms18050931>.
131. Rosch G, El Bagdadi K, Muschter D, Taheri S, Dorn C, Meurer A, et al. Sympathectomy aggravates subchondral bone changes during osteoarthritis progression in mice without affecting cartilage degeneration or synovial inflammation. *Osteoarthr Cartilage.* 2022;30(3):461-74. <https://doi.org/10.1016/j.joca.2021.11.016>.
132. Glasson SS, Blanchet TJ, Morris EA. The surgical destabilization of

- the medial meniscus (DMM) model of osteoarthritis in the 129/SvEv mouse. *Osteoarthr Cartilage*. 2007;15(9):1061-9. <https://doi.org/10.1016/j.joca.2007.03.006>.
133. Speichert S, Molotkov N, El Bagdadi K, Meurer A, Zaucke F, Jenei-Lanzl Z. Role of norepinephrine in IL-1 β -induced chondrocyte dedifferentiation under physioxia. *Int J Mol Sci*. 2019;20(5):1212. <https://doi.org/10.3390/ijms20051212>.
 134. Sohn R, Rosch G, Junker M, Meurer A, Zaucke F, Jenei-Lanzl Z. Adrenergic signalling in osteoarthritis. *Cell Signal*. 2021;82(82):109948. <https://doi.org/10.1016/j.cellsig.2021.109948>.
 135. Mitchell J, Lai LP, Peralta F, Xu Y, Sugamori K. β 2-adrenergic receptors inhibit the expression of collagen type II in growth plate chondrocytes by stimulating the AP-1 factor Jun-B. *Am J Physiol Endocrinol Metab*. 2011;300(4):E633-9. <https://doi.org/10.1152/ajpendo.00515.2010>.
 136. Guan Z, Liu Y, Luo L, Jin X, Guan Z, Yang J, et al. Sympathetic innervation induces exosomal miR-125 transfer from osteoarthritic chondrocytes, disrupting subchondral bone homeostasis and aggravating cartilage damage in aging mice. *J Adv Res*. 2025;69(69):245-60. <https://doi.org/10.1016/j.jare.2024.03.022>.
 137. Takarada T, Hojo H, Iemata M, Sahara K, Kodama A, Nakamura N, et al. Interference by adrenaline with chondrogenic differentiation through suppression of gene transactivation mediated by Sox9 family members. *Bone*. 2009;45(3):568-78. <https://doi.org/10.1016/j.bone.2009.05.004>.
 138. Figenschau Y, Knutsen G, Shahazeydi S, Johansen O, Sveinbjornsson B. Human articular chondrocytes express functional leptin receptors. *Biochem Biophys Res Commun*. 2001;287(1):190-7. <https://doi.org/10.1006/bbrc.2001.5543>.
 139. Kishida Y, Hirao M, Tamai N, Nampei A, Fujimoto T, Nakase T, et al. Leptin regulates chondrocyte differentiation and matrix maturation during endochondral ossification. *Bone*. 2005;37(5):607-21. <https://doi.org/10.1016/j.bone.2005.05.009>.
 140. Maor G, Rochwerger M, Segev Y, Phillip M. Leptin acts as a growth factor on the chondrocytes of skeletal growth centers. *J Bone Miner Res*. 2002;17(6):1034-43. <https://doi.org/10.1359/jbmr.2002.17.6.1034>.
 141. Kamatani T, Hagizawa H, Yarimitsu S, Morioka M, Koyamatsu S, Sugimoto M, et al. Human iPS cell-derived cartilaginous tissue spatially and functionally replaces nucleus pulposus. *Biomaterials*. 2022;284(284):121491. <https://doi.org/10.1016/j.biomaterials.2022.121491>.
 142. Luo Z, Wei Z, Zhang G, Chen H, Li L, Kang X. Achilles' heel-the significance of maintaining microenvironmental homeostasis in the nucleus pulposus for intervertebral discs. *Int J Mol Sci*. 2023;24(23):16592. <https://doi.org/10.3390/ijms242316592>.
 143. Guerrero J, Hackel S, Croft AS, Hoppe S, Albers CE, Gantenbein B. The nucleus pulposus microenvironment in the intervertebral disc: the fountain of youth? *Eur Cell Mater*. 2021;41(41):707-38. <https://doi.org/10.22203/eCM.v041a46>.
 144. Tian S, Chen X, Wu W, Lin H, Qing X, Liu S, et al. Nucleus pulposus cells regulate macrophages in degenerated intervertebral discs via the integrated stress response-mediated CCL2/7-CCR2 signaling pathway. *Exp Mol Med*. 2024;56(2):408-21. <https://doi.org/10.1038/s12276-024-01168-4>.
 145. Ahmed M, Bjurholm A, Kreicbergs A, Schultzberg M. Neuropeptide Y, tyrosine hydroxylase and vasoactive intestinal polypeptide-immunoreactive nerve fibers in the vertebral bodies, discs, dura mater, and spinal ligaments of the rat lumbar spine. *Spine (Phila Pa 1976)*. 1993;18(2):268-73. <https://doi.org/10.1097/00007632-199302000-00016>.
 146. Barczewska M, Juranek J, Wojtkiewicz J. Origins and neurochemical characteristics of porcine intervertebral disc sympathetic innervation: a preliminary report. *J Mol Neurosci*. 2017;63(1):50-7. <https://doi.org/10.1007/s12031-017-0956-3>.
 147. Kupka J, Kohler A, El Bagdadi K, Bostelmann R, Brenneis M, Fleege C, et al. Adrenoceptor expression during intervertebral disc degeneration. *Int J Mol Sci*. 2020;21(6):2085. <https://doi.org/10.3390/ijms21062085>.
 148. Liu W, Chen W, Xie M, Chen C, Shao Z, Zhang Y, et al. Traumatic brain injury stimulates sympathetic tone-mediated bone marrow myelopoiesis to favor fracture healing. *Signal Transduct Target Ther*. 2023;8(1):260. <https://doi.org/10.1038/s41392-023-01457-w>.
 149. Mehrotra M, Williams CR, Ogawa M, LaRue AC. Hematopoietic stem cells give rise to osteo-chondrogenic cells. *Blood Cells Mol Dis*. 2013;50(1):41-9. <https://doi.org/10.1016/j.bcmd.2012.08.003>.
 150. Shi SX, Shi K, Liu Q. Brain injury instructs bone marrow cellular lineage destination to reduce neuroinflammation. *Sci Transl Med*. 2021;13(589):eabc7029. <https://doi.org/10.1126/scitranslmed.abc7029>.
 151. Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, Zaltsman A, et al. Chronic variable stress activates hematopoietic stem cells. *Nat Med*. 2014;20(7):754-8. <https://doi.org/10.1038/nm.3589>.
 152. Maryanovich M, Zahalka AH, Pierce H, Pinho S, Nakahara F, Asada N, et al. Adrenergic nerve degeneration in bone marrow drives aging of the hematopoietic stem cell niche. *Nat Med*. 2018;24(6):782-91. <https://doi.org/10.1038/s41591-018-0030-x>.
 153. Park MH, Lee JK, Kim N, Min WK, Lee JE, Kim KT, et al. Neuropeptide Y induces hematopoietic stem/progenitor cell mobilization by regulating matrix metalloproteinase-9 activity through Y1 receptor in osteoblasts. *Stem Cells*. 2016;34(8):2145-56. <https://doi.org/10.1002/stem.2383>.
 154. Marinelli Busilacchi E, Morsia E, Poloni A. Bone marrow adipose tissue. *Cells*. 2024;13(9):724. <https://doi.org/10.3390/cells13090724>.
 155. Robles H, Park S, Joens MS, Fitzpatrick JAJ, Craft CS, Scheller EL. Characterization of the bone marrow adipocyte niche with three-dimensional electron microscopy. *Bone*. 2019;118(118):89-98. <https://doi.org/10.1016/j.bone.2018.01.020>.
 156. Lorenz MR, Brazill JM, Beeve AT, Shen I, Scheller EL. A neuroskeletal atlas: spatial mapping and contextualization of axon subtypes innervating the long bones of C3H and B6 mice. *J Bone Miner Res*. 2021;36(5):1012-25. <https://doi.org/10.1002/jbmr.4273>.
 157. Zeng W, Pirzgalska RM, Pereira MM, Kubasova N, Barateiro A, Seixas E, et al. Sympathetic neuro-adipose connections mediate leptin-driven lipolysis. *Cell*. 2015;163(1):84-94. <https://doi.org/10.1016/j.cell.2015.08.055>.
 158. Collins S. Beta-adrenoceptor signaling networks in adipocytes for recruiting stored fat and energy expenditure. *Front Endocrinol (Lausanne)*. 2011;2(2):102. <https://doi.org/10.3389/fendo.2011.00102>.
 159. Brasaemle DL. Thematic review series: adipocyte biology. The perilipin family of structural lipid droplet proteins: stabilization of lipid droplets and control of lipolysis. *J Lipid Res*. 2007;48(12):2547-59. <https://doi.org/10.1194/jlr.R700014-JLR200>.
 160. Bartness TJ, Liu Y, Shrestha YB, Ryu V. Neural innervation of white adipose tissue and the control of lipolysis. *Front Neuroendocrinol*.

- 2014;35(4):473-93. <https://doi.org/10.1016/j.yfrne.2014.04.001>.
161. Hauner H, Glatting G, Kaminska D, Pfeiffer EF. Effect of vasoactive intestinal polypeptide (VIP) on glucose and lipid metabolism of isolated rat adipocytes. *Res Exp Med* 1988;188(3):189-95. <https://doi.org/10.1007/BF01852320>.
162. Richter WO, Robl H, Schwandt P. Human glucagon and vasoactive intestinal polypeptide (VIP) stimulate free fatty acid release from human adipose tissue *in vitro*. *Peptides*. 1989;10(2):333-5. [https://doi.org/10.1016/0196-9781\(89\)90039-9](https://doi.org/10.1016/0196-9781(89)90039-9).
163. Huang T, Wan L, Chen Y, Xiong Y, Yuan F, Xie S, et al. The effect of local sympatholysis on bone-tendon interface healing in a murine rotator cuff repair model. *J Orthop Translat*. 2023;40(40):1-12. <https://doi.org/10.1016/j.jot.2023.03.001>.
164. Ackermann PW, Franklin SL, Dean BJ, Carr AJ, Salo PT, Hart DA. Neuronal pathways in tendon healing and tendinopathy—update. *Front Biosci* 2014;19(8):1251-78. <https://doi.org/10.2741/4280>.
165. Alpantaki K, McLaughlin D, Karagogeos D, Hadjipavlou A, Kontakis G. Sympathetic and sensory neural elements in the tendon of the long head of the biceps. *J Bone Joint Surg Am*. 2005;87(7):1580-3. <https://doi.org/10.2106/JBJS.D.02840>.
166. Fong G, Backman LJ, Andersson G, Scott A, Danielson P. Human tenocytes are stimulated to proliferate by acetylcholine through an EGFR signalling pathway. *Cell Tissue Res*. 2013;351(3):465-75. <https://doi.org/10.1007/s00441-012-1530-5>.
167. Sun K, Jiang J, Wang Y, Sun X, Zhu J, Xu X, et al. The role of nerve fibers and their neurotransmitters in regulating intervertebral disc degeneration. *Ageing Res Rev*. 2022;81(81):101733. <https://doi.org/10.1016/j.arr.2022.101733>.
168. Zhang C, Yu H, Miao Y, Wei B. Causal relationship between osteoporosis, bone mineral density, and osteonecrosis: a bidirectional two-sample Mendelian randomization study. *J Transl Med*. 2025;23(1):226. <https://doi.org/10.1186/s12967-024-06030-9>.
169. Dong Q, Luo G, Lane NE, Lui LY, Marshall LM, Kado DM, et al. Deep learning classification of spinal osteoporotic compression fractures on radiographs using an adaptation of the genant semiquantitative criteria. *Acad Radiol*. 2022;29(12):1819-32. <https://doi.org/10.1016/j.acra.2022.02.020>.
170. Clouse G, Penman S, Hadjiargyrou M, Komatsu DE, Thanos PK. Examining the role of cannabinoids on osteoporosis: a review. *Arch Osteoporos*. 2022;17(1):146. <https://doi.org/10.1007/s11657-022-01190-x>.
171. Zhang W, Luo Y, Xu J, Guo C, Shi J, Li L, et al. The possible role of electrical stimulation in osteoporosis: a narrative review. *Medicina*. 2023;59(1):121. <https://doi.org/10.3390/medicina59010121>.
172. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2022;33(10):2049-102. <https://doi.org/10.1007/s00198-021-05900-y>.
173. Zhong XP, Xia WF. Regulation of bone metabolism mediated by beta-adrenergic receptor and its clinical application. *World J Clin Cases*. 2021;9(30):8967-73. <https://doi.org/10.12998/wjcc.v9.i30.8967>.
174. Zhang W, Liu Y, Xu J, Fan C, Zhang B, Feng P, et al. The role of sympathetic nerves in osteoporosis: a narrative review. *Biomedicines*. 2022;11(1):33. <https://doi.org/10.3390/biomedicines11010033>.
175. Dani JA, Bertrand D. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. *Annu Rev Pharmacol Toxicol*. 2007;47(47):699-729. <https://doi.org/10.1146/annurev.pharmtox.47.120505.105214>.
176. Zhang J, Chen F, Yun F, Chen J. Low level nicotine: a novel approach to reduce osteoporosis incidence. *Med Hypotheses*. 2010;74(6):1067-8. <https://doi.org/10.1016/j.mehy.2009.12.024>.
177. Ma Y, Eleftheriou F. Brain-derived acetylcholine maintains peak bone mass in adult female mice. *J Bone Miner Res*. 2020;35(8):1562-71. <https://doi.org/10.1002/jbmr.4024>.
178. Meah F, Lundholm M, Emanuele N, Amjed H, Poku C, Agrawal L, et al. The effects of cannabis and cannabinoids on the endocrine system. *Rev Endocr Metab Disord*. 2022;23(3):401-20. <https://doi.org/10.1007/s11154-021-09682-w>.
179. Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI. Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest*. 1997;100(2):270-8. <https://doi.org/10.1172/JCI119532>.
180. Bartell SM, Rayalam S, Ambati S, Gaddam DR, Hartzell DL, Hamrick M, et al. Central (ICV) leptin injection increases bone formation, bone mineral density, muscle mass, serum IGF-1, and the expression of osteogenic genes in leptin-deficient ob/ob mice. *J Bone Miner Res*. 2011;26(8):1710-20. <https://doi.org/10.1002/jbmr.406>.
181. Caron A, Lee S, Elmquist JK, Gautron L. Leptin and brain-adipose crosstalks. *Nat Rev Neurosci*. 2018;19(3):153-65. <https://doi.org/10.1038/nrn.2018.7>.
182. Reid IR, Cornish J, Baldock PA. Nutrition-related peptides and bone homeostasis. *J Bone Miner Res*. 2006;21(4):495-500. <https://doi.org/10.1359/jbmr.051105>.
183. He Q, Qin R, Glowacki J, Zhou S, Shi J, Wang S, et al. Synergistic stimulation of osteoblast differentiation of rat mesenchymal stem cells by leptin and 25(OH)D₃ is mediated by inhibition of chaperone-mediated autophagy. *Stem Cell Res Ther*. 2021;12(1):557. <https://doi.org/10.1186/s13287-021-02623-z>.
184. Roux C, Arabi A, Porcher R, Garnero P. Serum leptin as a determinant of bone resorption in healthy postmenopausal women. *Bone*. 2003;33(5):847-52. <https://doi.org/10.1016/j.bone.2003.07.008>.
185. Maetani M, Maskarinec G, Franke AA, Cooney RV. Association of leptin, 25-hydroxyvitamin D, and parathyroid hormone in women. *Nutr Cancer*. 2009;61(2):225-31. <https://doi.org/10.1080/01635580802455149>.
186. Kulpa J, Harrison A, Rudolph L, Eglit GML, Turcotte C, Bonn-Miller MO, et al. Oral cannabidiol treatment in two postmenopausal women with osteopenia: a case series. *Cannabis Cannabinoid Res*. 2023;8(S1):S83-S9. <https://doi.org/10.1089/can.2023.0060>.
187. Khosla S, Drake MT, Volkman TL, Thicke BS, Achenbach SJ, Atkinson EJ, et al. Sympathetic beta1-adrenergic signaling contributes to regulation of human bone metabolism. *J Clin Invest*. 2018;128(11):4832-42. <https://doi.org/10.1172/JCI122151>.
188. Bonnet N, Gadois C, McCloskey E, Lemineur G, Lespessailles E, Courteix D, et al. Protective effect of beta blockers in postmenopausal women: influence on fractures, bone density, micro and macroarchitecture. *Bone*. 2007;40(5):1209-16. <https://doi.org/10.1016/j.bone.2007.01.006>.
189. Rejnmark L, Vestergaard P, Mosekilde L. Treatment with beta-blockers, ACE inhibitors, and calcium-channel blockers is associated with a reduced fracture risk: a nationwide case-control study. *J Hypertens*. 2006;24(3):581-9. <https://doi.org/10.1097/01.hjh.0000203845.26690.cb>.
190. Heikkinen AM, Niskanen LK, Salmi JA, Koulou M, Pesonen U, Uusitupa MI, et al. Leucine7 to proline7 polymorphism in prepro-NPY gene and femoral neck bone mineral density in

- postmenopausal women. *Bone*. 2004;35(3):589-94. <https://doi.org/10.1016/j.bone.2004.05.004>.
191. Kim BJ, Kwak MK, Kim JS, Lee SH, Koh JM. Higher sympathetic activity as a risk factor for skeletal deterioration in pheochromocytoma. *Bone*. 2018;116(116):1-7. <https://doi.org/10.1016/j.bone.2018.06.023>.
 192. Tosun A, Dogru MT, Aydn G, Keles I, Arslan A, Guneri M, et al. Does autonomic dysfunction exist in postmenopausal osteoporosis?. *Am J Phys Med Rehabil*. 2011;90(12):1012-9. <https://doi.org/10.1097/PHM.0b013e31822dea1a>.
 193. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthr Cartilage*. 2015;23(8):1233-41. <https://doi.org/10.1016/j.joca.2015.03.036>.
 194. Collaborators GBDLBP. Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol*. 2023;5(6):e316-e29. [https://doi.org/10.1016/S2665-9913\(23\)00098-X](https://doi.org/10.1016/S2665-9913(23)00098-X).
 195. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet*. 2019;393(10182):1745-59. [https://doi.org/10.1016/S0140-6736\(19\)30417-9](https://doi.org/10.1016/S0140-6736(19)30417-9).
 196. Kloppenburg M, Kroon FP, Blanco FJ, Doherty M, Dziedzic KS, Greibrokk E, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis*. 2019;78(1):16-24. <https://doi.org/10.1136/annrheumdis-2018-213826>.
 197. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-33. <https://doi.org/10.1002/art.41142>.
 198. Kloppenburg M, Namane M, Cicuttini F. Osteoarthritis. *Lancet*. 2025;405(10472):71-85. [https://doi.org/10.1016/S0140-6736\(24\)02322-5](https://doi.org/10.1016/S0140-6736(24)02322-5).
 199. Xie J, Strauss VY, Martinez-Laguna D, Carbonell-Abella C, Diez-Perez A, Nogues X, et al. Association of tramadol vs. codeine prescription dispensation with mortality and other adverse clinical outcomes. *JAMA*. 2021;326(15):1504-15. <https://doi.org/10.1001/jama.2021.15255>.
 200. Cruz CJ, Dewberry LS, Otto KJ, Allen KD. Neuromodulation as a potential disease-modifying therapy for osteoarthritis. *Curr Rheumatol Rep*. 2023;25(1):1-11. <https://doi.org/10.1007/s11926-022-01094-2>.
 201. Jiao K, Niu LN, Li QH, Ren GT, Zhao CM, Liu YD, et al. beta2-Adrenergic signal transduction plays a detrimental role in subchondral bone loss of temporomandibular joint in osteoarthritis. *Sci Rep*. 2015;5(5):12593. <https://doi.org/10.1038/srep12593>.
 202. Teng P, Liu Y, Dai Y, Zhang H, Liu WT, Hu J. Nicotine attenuates osteoarthritis pain and matrix metalloproteinase-9 expression via the alpha7 nicotinic acetylcholine receptor. *J Immunol*. 2019;203(2):485-92. <https://doi.org/10.4049/jimmunol.1801513>.
 203. Kawakita A, Sato K, Makino H, Ikegami H, Takayama S, Toyama Y, et al. Nicotine acts on growth plate chondrocytes to delay skeletal growth through the alpha7 neuronal nicotinic acetylcholine receptor. *PLoS One*. 2008;3(12):e3945. <https://doi.org/10.1371/journal.pone.0003945>.
 204. Burr DB, Gallant MA. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol*. 2012;8(11):665-73. <https://doi.org/10.1038/nrrheum.2012.130>.
 205. Neogi T. Clinical significance of bone changes in osteoarthritis. *Ther Adv Musculoskelet Dis*. 2012;4(4):259-67. <https://doi.org/10.1177/1759720X12437354>.
 206. Rosch G, Zaucke F, Jenei-Lanzl Z. Autonomic nervous regulation of cellular processes during subchondral bone remodeling in osteoarthritis. *Am J Physiol Cell Physiol*. 2023;325(2):C365-C84. <https://doi.org/10.1152/ajpcell.00039.2023>.
 207. Rosch G, Muschter D, Taheri S, El Bagdadi K, Dorn C, Meurer A, et al. Beta2-adrenoceptor deficiency results in increased calcified cartilage thickness and subchondral bone remodeling in murine experimental osteoarthritis. *Front Immunol*. 2021;12(12):801505. <https://doi.org/10.3389/fimmu.2021.801505>.
 208. Delgado M, Pozo D, Ganea D. The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev*. 2004;56(2):249-90. <https://doi.org/10.1124/pr.56.2.7>.
 209. Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. *J Pain*. 2008;9(2):122-45. <https://doi.org/10.1016/j.jpain.2007.09.006>.
 210. Jiang W, Wang H, Li YS, Luo W. Role of vasoactive intestinal peptide in osteoarthritis. *J Biomed Sci*. 2016;23(1):63. <https://doi.org/10.1186/s12929-016-0280-1>.
 211. Delgado M, Abad C, Martinez C, Leceta J, Gomariz RP. Vasoactive intestinal peptide prevents experimental arthritis by downregulating both autoimmune and inflammatory components of the disease. *Nat Med*. 2001;7(5):563-8. <https://doi.org/10.1038/87887>.
 212. Jenei-Lanzl Z, Grassel S, Pongratz G, Kees F, Miosge N, Angele P, et al. Norepinephrine inhibition of mesenchymal stem cell and chondrogenic progenitor cell chondrogenesis and acceleration of chondrogenic hypertrophy. *Arthritis Rheumatol*. 2014;66(9):2472-81. <https://doi.org/10.1002/art.38695>.
 213. Vonk LA, van Dooremalen SFJ, Liv N, Klumperman J, Coffey PJ, Saris DBF, et al. Mesenchymal stromal/stem cell-derived extracellular vesicles promote human cartilage regeneration *in vitro*. *Theranostics*. 2018;8(4):906-20. <https://doi.org/10.7150/thno.20746>.
 214. Lee YC, Massarotti E, Edwards RR, Lu B, Liu C, Lo Y, et al. Effect of milnacipran on pain in patients with rheumatoid arthritis with widespread pain: a randomized blinded crossover trial. *J Rheumatol*. 2016;43(1):38-45. <https://doi.org/10.3899/jrheum.150550>.
 215. Courties A, Berenbaum F, Sellam J. Vagus nerve stimulation in musculoskeletal diseases. *Joint Bone Spine*. 2021;88(3):105149. <https://doi.org/10.1016/j.jbspin.2021.105149>.
 216. Aoyagi K, Rivas E, Shababi R, Edwards R, LaValley M, Lechuga J, et al. Safety and preliminary efficacy of transcutaneous auricular vagus nerve stimulation on chronic knee pain: a pilot trial. *Osteoarthr Cartil Open*. 2025;7(1):100545. <https://doi.org/10.1016/j.jocarto.2024.100545>.
 217. Augat P, von Ruden C. Evolution of fracture treatment with bone plates. *Injury*. 2018;49 Suppl 1(S2-S7). [https://doi.org/10.1016/S0020-1383\(18\)30294-8](https://doi.org/10.1016/S0020-1383(18)30294-8).
 218. Parker RS, Nazzari MK, Morris AJ, Fehrenbacher JC, White FA, Kacena MA, et al. Role of the neurologic system in fracture healing: an extensive review. *Curr Osteoporos Rep*. 2024;22(1):205-16. <https://doi.org/10.1007/s11914-023-00844-0>.
 219. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet*. 2019;393(10169):364-76. [https://doi.org/10.1016/S0140-6736\(19\)30417-9](https://doi.org/10.1016/S0140-6736(19)30417-9).

- 6736(18)32112-3.
220. Collaborators GBDF. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet Healthy Longev.* 2021;2(9):e580–e92. [https://doi.org/10.1016/S2666-7568\(21\)00172-0](https://doi.org/10.1016/S2666-7568(21)00172-0).
221. Chartier SR, Thompson ML, Longo G, Fealk MN, Majuta LA, Mantyh PW. Exuberant sprouting of sensory and sympathetic nerve fibers in nonhealed bone fractures and the generation and maintenance of chronic skeletal pain. *Pain.* 2014;155(11):2323–36. <https://doi.org/10.1016/j.pain.2014.08.026>.
222. Wildemann B, Ignatius A, Leung F, Taitsman LA, Smith RM, Pesantez R, et al. Non-union bone fractures. *Nat Rev Dis Primers.* 2021;7(1):57. <https://doi.org/10.1038/s41572-021-00289-8>.
223. Ekegren CL, Edwards ER, de Steiger R, Gabbe BJ. Incidence, costs and predictors of non-union, delayed union and mal-union following long bone fracture. *Int J Environ Res Public Health.* 2018;15(12):2845. <https://doi.org/10.3390/ijerph15122845>.
224. Nazzal MK, Morris AJ, Parker RS, White FA, Natoli RM, Kacena MA, et al. Do not lose your nerve, be callus: insights into neural regulation of fracture healing. *Curr Osteoporos Rep.* 2024;22(1):182–92. <https://doi.org/10.1007/s11914-023-00850-2>.
225. Wagner JM, Wallner C, Becerikli M, Reinkemeier F, von Glinzki M, Sogorski A, et al. Role of autonomous neuropathy in diabetic bone regeneration. *Cells.* 2022;11(4):612. <https://doi.org/10.3390/cells11040612>.
226. Wank I, Niedermair T, Kronenberg D, Stange R, Brochhausen C, Hess A, et al. Influence of the peripheral nervous system on murine osteoporotic fracture healing and fracture-induced hyperalgesia. *Int J Mol Sci.* 2022;24(1):510. <https://doi.org/10.3390/ijms24010510>.
227. Niedermair T, Straub RH, Brochhausen C, Grassel S. Impact of the sensory and sympathetic nervous system on fracture healing in ovariectomized mice. *Int J Mol Sci.* 2020;21(2):405. <https://doi.org/10.3390/ijms21020405>.
228. Niedermair T, Kuhn V, Doranehgard F, Stange R, Wieskotter B, Beckmann J, et al. Absence of substance P and the sympathetic nervous system impact on bone structure and chondrocyte differentiation in an adult model of endochondral ossification. *Matrix Biol.* 2014;38(38):22–35. <https://doi.org/10.1016/j.matbio.2014.06.007>.
229. Stegen S, van Gastel N, Carmeliet G. Bringing new life to damaged bone: the importance of angiogenesis in bone repair and regeneration. *Bone.* 2015;70(70):19–27. <https://doi.org/10.1016/j.bone.2014.09.017>.
230. Kusumbe AP, Ramasamy SK, Adams RH. Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. *Nature.* 2014;507(7492):323–8. <https://doi.org/10.1038/nature13145>.
231. Jahn D, Knapstein PR, Otto E, Kohli P, Sevecke J, Graef F, et al. Increased beta2-adrenergic signaling promotes fracture healing through callus neovascularization in mice. *Sci Transl Med.* 2024;16(743):eadk9129. <https://doi.org/10.1126/scitranslmed.adk9129>.
232. Sahbaie P, Li WW, Guo TZ, Shi XY, Kingery WS, Clark JD. Autonomic regulation of nociceptive and immunologic changes in a mouse model of complex regional pain syndrome. *J Pain.* 2022;23(3):472–86. <https://doi.org/10.1016/j.jpain.2021.09.009>.
233. Kumar N, Thapa D, Gombor S, Ahuja V, Gupta R. Analgesic efficacy of pre-operative stellate ganglion block on postoperative pain relief: a randomised controlled trial. *Anaesthesia.* 2014;69(9):954–660. <https://doi.org/10.1111/anae.12774>.
234. Garbe A, Graef F, Appelt J, Schmidt-Bleek K, Jahn D, Lunnemann T, et al. Leptin mediated pathways stabilize posttraumatic insulin and osteocalcin patterns after long bone fracture and concomitant traumatic brain injury and thus influence fracture healing in a combined murine trauma model. *Int J Mol Sci.* 2020;21(23):9144. <https://doi.org/10.3390/ijms21239144>.
235. Hofman M, Koopmans G, Kobbe P, Poeze M, Andruszkow H, Brink PR, et al. Improved fracture healing in patients with concomitant traumatic brain injury: proven or not?. *Mediators Inflamm.* 2015;2015(2015):204842. <https://doi.org/10.1155/2015/204842>.
236. Wei Y, Wang L, Clark JC, Dass CR, Choong PF. Elevated leptin expression in a rat model of fracture and traumatic brain injury. *J Pharm Pharmacol.* 2008;60(12):1667–72. <https://doi.org/10.1211/jpp/60.12.0013>.
237. Long H, Ahmed M, Ackermann P, Stark A, Li J. Neuropeptide Y innervation during fracture healing and remodeling. A study of angulated tibial fractures in the rat. *Acta Orthop.* 2010;81(5):639–46. <https://doi.org/10.3109/17453674.2010.504609>.
238. Sousa DM, McDonald MM, Mikulec K, Peacock L, Herzog H, Lamghari M, et al. Neuropeptide Y modulates fracture healing through Y1 receptor signaling. *J Orthop Res.* 2013;31(10):1570–8. <https://doi.org/10.1002/jor.22400>.
239. Bjurholm A, Kreicbergs A, Terenius L, Goldstein M, Schultzberg M. Neuropeptide Y-, tyrosine hydroxylase- and vasoactive intestinal polypeptide-immunoreactive nerves in bone and surrounding tissues. *J Auton Nerv Syst.* 1988;25(2-3):119–25. [https://doi.org/10.1016/0165-1838\(88\)90016-1](https://doi.org/10.1016/0165-1838(88)90016-1).
240. Hill EL, Elde R. Distribution of CGRP-, VIP-, Dβ H-, SP-, and NPY-immunoreactive nerves in the periosteum of the rat. *Cell Tissue Res.* 1991;264(3):469–80. <https://doi.org/10.1007/BF00319037>.
241. Gu XC, Zhang XB, Hu B, Zi Y, Li M. Neuropeptide Y accelerates post-fracture bone healing by promoting osteogenesis of mesenchymal stem cells. *Neuropeptides.* 2016;60(60):61–6. <https://doi.org/10.1016/j.npep.2016.09.005>.
242. Lundberg P, Allison SJ, Lee NJ, Baldock PA, Brouard N, Rost S, et al. Greater bone formation of Y2 knockout mice is associated with increased osteoprogenitor numbers and altered Y1 receptor expression. *J Biol Chem.* 2007;282(26):19082–91. <https://doi.org/10.1074/jbc.M609629200>.
243. Park EH, Moon SW, Suh HR, Hochman S, Lee MG, Kim YI, et al. Disc degeneration induces a mechano-sensitization of disc afferent nerve fibers that associates with low back pain. *Osteoarthritis Cartilage.* 2019;27(11):1608–17. <https://doi.org/10.1016/j.joca.2019.07.010>.
244. Francisco V, Pino J, Gonzalez-Gay MA, Lago F, Karppinen J, Tervonen O, et al. A new immunometabolic perspective of intervertebral disc degeneration. *Nat Rev Rheumatol.* 2022;18(1):47–60. <https://doi.org/10.1038/s41584-021-00713-z>.
245. Yang S, Zhang F, Ma J, Ding W. Intervertebral disc ageing and degeneration: the antiapoptotic effect of oestrogen. *Ageing Res Rev.* 2020;57(57):100978. <https://doi.org/10.1016/j.arr.2019.100978>.
246. Li Y, Dai C, Wu B, Yang L, Yan X, Liu T, et al. Intervertebral disc injury triggers neurogenic inflammation of adjacent healthy discs. *Spine J.* 2024;24(8):1527–37. <https://doi.org/10.1016/j.spinee.2024.04.002>.
247. Zhang C, Xin X, Qi P, Sheng T, Liu Z, Yang L, et al. A patient with lumbar disc herniation complicates cauda equina syndrome after epidural steroid injection: a case report. *Medicine (Baltimore).* 2026;105(20):e48739. <https://doi.org/10.1097/>

- MD.0000000000048739.
248. Rustenburg CME, Emanuel KS, Peeters M, Lems WF, Vergroesen PA, Smit TH. Osteoarthritis and intervertebral disc degeneration: quite different, quite similar. *JOR Spine*. 2018;1(4):e1033. <https://doi.org/10.1002/jsp2.1033>.
 249. Edgar MA. The nerve supply of the lumbar intervertebral disc. *J Bone Joint Surg Br*. 2007;89(9):1135-9. <https://doi.org/10.1302/0301-620X.89B9.18939>.
 250. Raj PP. Intervertebral disc: anatomy-physiology-pathophysiology-treatment. *Pain Pract*. 2008;8(1):18-44. <https://doi.org/10.1111/j.1533-2500.2007.00171.x>.
 251. Fujimoto K, Miyagi M, Ishikawa T, Inoue G, Eguchi Y, Kamoda H, et al. Sensory and autonomic innervation of the cervical intervertebral disc in rats: the pathomechanics of chronic discogenic neck pain. *Spine*. 2012;37(16):1357-62. <https://doi.org/10.1097/BRS.0b013e31824ba710>.
 252. Brenneis M, Jenei-Lanzl Z, Kupka J, Braun S, Junker M, Zaucke F, et al. Correlation between adrenoceptor expression and clinical parameters in degenerated lumbar intervertebral discs. *Int J Mol Sci*. 2022;23(23):15358. <https://doi.org/10.3390/ijms232315358>.
 253. Diaz-delCastillo M, Woldbye DPD, Heegaard AM. Neuropeptide Y and its involvement in chronic pain. *Neuroscience*. 2018;387(387):162-9. <https://doi.org/10.1016/j.neuroscience.2017.08.050>.
 254. Fu W, Nelson TS, Santos DF, Doolen S, Gutierrez JJP, Ye N, et al. An NPY Y1 receptor antagonist unmasks latent sensitization and reveals the contribution of protein kinase A and Epac to chronic inflammatory pain. *Pain*. 2019;160(8):1754-65. <https://doi.org/10.1097/j.pain.0000000000001557>.
 255. Navarro-Ledesma S, Hamed-Hamed D, Pruijboom L. A new perspective of frozen shoulder pathology; the interplay between the brain and the immune system. *Front Physiol*. 2024; 15:1248612. <https://doi.org/10.3389/fphys.2024.1248612>.
 256. Picasso R, Pistoia F, Zaottini F, Marcenaro G, Miguel-Perez M, Tagliafico AS, et al. Adhesive capsulitis of the shoulder: current concepts on the diagnostic work-up and evidence-based protocol for radiological evaluation. *Diagnostics (Basel)*. 2023;13(22):3410. <https://doi.org/10.3390/diagnostics13223410>.
 257. Mertens MG, Struyf F, Lluch Girbes E, Duenas L, Verborcht O, Meeus M. Autonomic nervous system function and central pain processing in people with frozen shoulder: a case-control study. *Clin J Pain*. 2022;38(11):659-69. <https://doi.org/10.1097/AJP.0000000000001070>.
 258. Mao JJ, Stosich MS, Moiola EK, Lee CH, Fu SY, Bastian B, et al. Facial reconstruction by biosurgery: cell transplantation versus cell homing. *Tissue Eng Part B Rev*. 2010;16(2):257-62. <https://doi.org/10.1089/ten.TEB.2009.0496>.
 259. Wang T, Cao J, Du ZJ, Zhang YB, Liu YP, Wang L, et al. Effects of sympathetic innervation loss on mandibular distraction osteogenesis. *J Craniofac Surg*. 2012;23(5):1524-8. <https://doi.org/10.1097/SCS.0b013e31825daab2>.
 260. Hu ZS, Zhao ZH, Tseng CC, Li J, Man GC, Lam TP, et al. Abnormal activity of sympathetic nervous system in girls with adolescent idiopathic scoliosis: a cross-sectional study. *Biomed Environ Sci*. 2018;31(9):700-4. <https://doi.org/10.3967/bes2018.094>.
 261. Scaturro D, Balbo A, Vitagliani F, Stramazzo L, Camarda L, Letizia Mauro G. Is there a relationship between idiopathic scoliosis and body mass? A scoping review. *Nutrients*. 2022;14(19):4011. <https://doi.org/10.3390/nu14194011>.
 262. Chen J, Hu Q, Hu J, Liu S, Yin L. Differences in the effectiveness of different physical therapy modalities in the treatment of delayed-onset muscle soreness: a systematic review and bayesian network meta-analysis. *J Pain Res*. 2025;18:2993-3008. <https://doi.org/10.2147/JPR.S519242>.
 263. Lewis PB, Ruby D, Bush-Joseph CA. Muscle soreness and delayed-onset muscle soreness. *Clin Sports Med*. 2012;31(2):255-62. <https://doi.org/10.1016/j.csm.2011.09.009>.
 264. Mizumura K, Taguchi T. Delayed onset muscle soreness: Involvement of neurotrophic factors. *J Physiol Sci*. 2016;66(1):43-52. <https://doi.org/10.1007/s12576-015-0397-0>.
 265. Fleckenstein J, Neuberger EWI, Bormuth P, Comes F, Schneider A, Banzer W, et al. Investigation of the sympathetic regulation in delayed onset muscle soreness: results of an RCT. *Front Physiol*. 2021;12(12):697335. <https://doi.org/10.3389/fphys.2021.697335>.
 266. Errani C, Bazzocchi A, Spinnato P, Facchini G, Campanacci L, Rossi G, et al. What's new in management of bone metastases?. *Eur J Orthop Surg Traumatol*. 2019;29(7):1367-75. <https://doi.org/10.1007/s00590-019-02446-y>.
 267. Ferguson JL, Turner SP. Bone cancer: diagnosis and treatment principles. *Am Fam Physician*. 2018;98(4):205-13. <https://www.aafp.org/afp/2018/0815/p205.pdf>.
 268. Hwa YL, Shi Q, Kumar SK, Lacy MQ, Gertz MA, Kapoor P, et al. Beta-blockers improve survival outcomes in patients with multiple myeloma: a retrospective evaluation. *Am J Hematol*. 2017; 92(1):50-5. <https://doi.org/10.1002/ajh.24582>.
 269. Hwa YL, Lacy MQ, Gertz MA, Kumar SK, Muchtar E, Buadi FK, et al. Use of beta blockers is associated with survival outcome of multiple myeloma patients treated with pomalidomide. *Eur J Haematol*. 2021;106(3):433-6. <https://doi.org/10.1111/ejh.13559>.
 270. Cheng Y, Sun F, D'Souza A, Dhakal B, Pisano M, Chhabra S, et al. Autonomic nervous system control of multiple myeloma. *Blood Rev*. 2021;46(4):100741. <https://doi.org/10.1016/j.blre.2020.100741>.
 271. Duckett MM, Phung SK, Nguyen L, Khammanivong A, Dickerson E, Dusenbery K, et al. The adrenergic receptor antagonists propranolol and carvedilol decrease bone sarcoma cell viability and sustained carvedilol reduces clonogenic survival and increases radiosensitivity in canine osteosarcoma cells. *Vet Comp Oncol*. 2020;18(1):128-40. <https://doi.org/10.1111/vco.12560>.
 272. Lu C, Mahajan A, Hong SH, Galli S, Zhu S, Tilan JU, et al. Hypoxia-activated neuropeptide Y/Y5 receptor/RhoA pathway triggers chromosomal instability and bone metastasis in Ewing sarcoma. *Nat Commun*. 2022;13(1):2323. <https://doi.org/10.1038/s41467-022-29898-x>.
 273. Adnani M, Hong SH, Galli S, Mahajan A, Lu C, Abualsaud N, et al. Targeted CRISPR approach reveals an essential role for neuropeptide Y receptor Y5 in Ewing sarcoma extrapulmonary metastasis. *Oncogene*. 2025;44(36):3350-63. <https://doi.org/10.1038/s41388-025-03493-y>.
 274. Conceicao F, Sousa DM, Paredes J, Lamghari M. Sympathetic activity in breast cancer and metastasis: partners in crime. *Bone Res*. 2021;9(1):9. <https://doi.org/10.1038/s41413-021-00137-1>.
 275. Campbell JP, Karolak MR, Ma Y, Perrien DS, Masood-Campbell SK, Penner NL, et al. Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. *PLoS Biol*. 2012;10(7):e1001363. <https://doi.org/10.1371/journal.pbio.1001363>.
 276. An J, Feng L, Ren J, Li Y, Li G, Liu C, et al. Chronic stress promotes breast carcinoma metastasis by accumulating myeloid-derived suppressor cells through activating beta-adrenergic signaling.

- Oncoimmunology. 2021;10(1):2004659. <https://doi.org/10.1080/2162402X.2021.2004659>.
277. Madel MB, Elefteriou F. Mechanisms Supporting the Use of Beta-blockers for the management of breast cancer bone metastasis. *Cancers (Basel)*. 2021;13(12):2887. <https://doi.org/10.3390/cancers13122887>.
 278. Zhang X, Lv X, Zhang Y, Jiao X, Chen B. Propranolol prevents osteoporosis and up-regulates leptin in ovariectomized rats. *Iran J Pharm Res*. 2013;12(3):557-62. <https://brieflands.com/journals/ijpr/articles/125689.pdf>.
 279. Sun JL, Yan JF, Li J, Wang WR, Yu SB, Zhang HY, et al. Conditional deletion of Ahrb2 in mesenchymal stem cells attenuates osteoarthritis-like defects in temporomandibular joint. *Bone*. 2020;133(133):115229. <https://doi.org/10.1016/j.bone.2020.115229>.
 280. L EW, Srinivasan S, Threet D, Ausk BJ, Huber P, R YK, et al. Beta 2 adrenergic receptor selective antagonist enhances mechanically stimulated bone anabolism in aged mice. *JBMR Plus*. 2023;7(2):e10712. <https://doi.org/10.1002/jbm4.10712>.
 281. Sun L, Kuang S, Wang C, Li Y, Wang G, Sun J, et al. IL-6 blockade at the fracture site accelerates bone healing via inflammatory modulation of sensory nerve CGRP signaling. *Int Immunopharmacol*. 2026;173:116258. <https://doi.org/10.1016/j.intimp.2026.116258>.
 282. Li Y, Zhai Y, Wang T, Wang S, Tian Y, Bian Z, et al. An anti-FAP-scFv-functionalized exosome-carrying hydrogel delivers SKI mRNA to fibrotic nucleus pulposus cells to alleviate intervertebral disc degeneration by regulating FOXO3. *Theranostics*. 2025;15(9):3877-99. <https://doi.org/10.7150/thno.107776>.
 283. Zhan J, Cui Y, Zhang P, Du Y, Hecker P, Zhou S, et al. Cartilage endplate-targeted engineered exosome releasing and acid neutralizing hydrogel reverses intervertebral disc degeneration. *Adv Healthc Mater*. 2025;14(2):e2403315. <https://doi.org/10.1002/adhm.202403315>.
 284. Chen X, Jing S, Xue C, Guan X. Progress in the application of hydrogels in intervertebral disc repair: a comprehensive review. *Curr Pain Headache Rep*. 2024;28(12):1333-48. <https://doi.org/10.1007/s11916-024-01296-6>.
 285. Ke W, Xu H, Zhang C, Liao Z, Liang H, Tong B, et al. An overview of mechanical microenvironment and mechanotransduction in intervertebral disc degeneration. *Exp Mol Med*. 2025;57(10):2157-68. <https://doi.org/10.1038/s12276-025-01546-6>.
 286. Morris AJ, Parker RS, Nazzal MK, Natoli RM, Fehrenbacher JC, Kacena MA, et al. Cracking the code: the role of peripheral nervous system signaling in fracture repair. *Curr Osteoporos Rep*. 2024;22(1):193-204. <https://doi.org/10.1007/s11914-023-00846-y>.
 287. Bataille C, Mauprivez C, Hay E, Baroukh B, Brun A, Chaussain C, et al. Different sympathetic pathways control the metabolism of distinct bone envelopes. *Bone*. 2012;50(5):1162-72. <https://doi.org/10.1016/j.bone.2012.01.023>.
 288. Iredahl F, Tesselaar E, Jonasson H, Wilhelms D, Henricson J. Concentration-dependent microvascular responses to repeated iontophoresis of acetylcholine. *Microvasc Res*. 2025;157:104749. <https://doi.org/10.1016/j.mvr.2024.104749>.
 289. Yeater TD, Cruz CJ, Cruz-Almeida Y, Allen KD. Autonomic nervous system dysregulation and osteoarthritis pain: mechanisms, measurement, and future outlook. *Curr Rheumatol Rep*. 2022;24(6):175-83. <https://doi.org/10.1007/s11926-022-01071-9>.
 290. Reisig F, Harnik M. [Neuropathic pain: pharmacotherapy]. *Ther Umsch*. 2020;77(6):274-80. <https://doi.org/10.1024/0040-5930/a001191>.
 291. Patel ABU, Weber V, Gourine AV, Ackland GL. The potential for autonomic neuromodulation to reduce perioperative complications and pain: a systematic review and meta-analysis. *Br J Anaesth*. 2022;128(1):135-49. <https://doi.org/10.1016/j.bja.2021.08.037>.

<https://doi.org/10.1016/j.mmr.2026.100051>

Cite this article as: Huang WJ, Hu YK, Li HZ, Lu WH, Yang G, Ji BZ, et al. From nerve to bone: a tale of autonomic nervous system, bone cells, and beyond. *Mil Med Res*. 2026;13(1):100051.