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■ **ARTHRITIS**

Peripheral nerves in the tibial subchondral bone

THE ROLE OF PAIN AND HOMEOSTASIS IN OSTEOARTHRITIS

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Osteoarthritis (OA) is a highly prevalent degenerative joint disorder characterized by joint pain and physical disability. Aberrant subchondral bone induces pathological changes and is a major source of pain in OA. In the subchondral bone, which is highly innervated, nerves have dual roles in pain sensation and bone homeostasis regulation. The interaction between peripheral nerves and target cells in the subchondral bone, and the interplay between the sensory and sympathetic nervous systems, allow peripheral nerves to regulate subchondral bone homeostasis. Alterations in peripheral innervation and local transmitters are closely related to changes in nociception and subchondral bone homeostasis, and affect the progression of OA. Recent literature has substantially expanded our understanding of the physiological and pathological distribution and function of specific subtypes of neurones in bone. This review summarizes the types and distribution of nerves detected in the tibial subchondral bone, their cellular and molecular interactions with bone cells that regulate subchondral bone homeostasis, and their role in OA pain. A comprehensive understanding and further investigation of the functions of peripheral innervation in the subchondral bone will help to develop novel therapeutic approaches to effectively prevent OA, and alleviate OA pain.

Article focus
- We review the effect of peripheral sensory and sympathetic nerves on bone homeostasis and the pathological changes found in osteoarthritic (OA) subchondral bone.
- We describe the mechanisms of regulation of subchondral bone by peripheral nerves in OA and pain generation.

Key messages
- Peripheral sensory and sympathetic nerves regulate subchondral bone homeostasis in both direct and indirect mechanisms.
- Uncoupled subchondral bone remodelling leads to altered distribution and activity of peripheral nerves.
- Altered sensory nerve function in subchondral bone has a key role in OA pain.

Strengths and limitations
- The type and distribution of nerves and the cellular and molecular interaction between bone cells and peripheral nerves in normal and OA subchondral bone are summarized.
- The role of interactions between sensory nerve and sympathetic nerves in the regulation of subchondral bone homeostasis and OA pain is reviewed; this may facilitate development of therapeutic strategies to treat OA pain.
- Research on modulation of peripheral nerves on subchondral bone homeostasis and pain generation is limited, and further work is required.

Introduction
Osteoarthritis (OA) is a degenerative joint disease that is highly prevalent worldwide, and is expected to affect more than 25% of

adults and to occur in over 67 million Americans by 2030.[1] OA presents an enormous clinical challenge and financial burden, and is a leading cause of joint pain and physical disability due to its effects on weightbearing joints, such as the knee and hip.[2-5] OA pain and joint dysfunction are commonly the main reasons that patients seek medical intervention. Pain itself is also a major risk factor for the development of future functional limitations and disability in OA patients.[6] However, there is still a lack of effective disease-modifying treatments for OA that achieve sustained pain relief and improve joint function before joint arthroplasty in end-stage OA. Therefore, it is necessary to comprehensively explore and understand the pathogenesis and pain mechanisms of OA, which will subsequently allow the development of effective treatments for OA.

The mechanisms of OA pain are multifactorial. Currently, synovial inflammation and cartilage degeneration are being intensively investigated for their roles in OA pain.[7-9] Nevertheless, OA pain can manifest at a very early stage in the absence of synovial inflammation and cartilage degeneration. Importantly, OA patients achieved rapid and obvious pain relief after the removal of the subchondral bone and overlying articular cartilage through total knee arthroplasty (TKA).[10,11] Articular cartilage, which typically lacks innervation,[12] is incapable of generating pain, indicating that the subchondral bone is a major source of OA pain. Additionally, subchondral bone marrow oedema-like lesions are highly correlated with OA pain.[13,14] Reduction of the size of bone marrow oedema-like lesions by inhibition of osteoclast activity concomitantly alleviated pain.[15] In OA, the occurrence of osteochondral junctions and osteophytes is commonly coupled with innervation and angiogenesis,[16] and they can be sources of pain in OA. OA pain is notably modulated by the purely peripherally acting nerve growth factor (NGF),[17] supporting the concept that continuous nociceptive input from joint nerves contributes substantially to OA pain. Specifically, aberrant sensory innervation and increased inflammatory stimulators, such as prostaglandin E2 (PGE2), induced by aberrant subchondral bone remodelling are responsible for OA pain.[18,19] The sensory nerve in the subchondral bone plays a critical role in OA pain.[20]

Aberrant subchondral bone remodelling and abnormal subchondral bone architecture are critical factors in pathological changes in OA,[3,21-23] although the aetiology of the initiation and progression of OA remains controversial. Aberrant subchondral bone microarchitecture disrupts the mechanical support of the overlying articular cartilage, and abnormal stress on the articular cartilage induces its degeneration.[24] Bone remodelling, which includes osteoclast-induced bone resorption coupled with osteoblast-induced bone formation, is essential to maintain the normal microarchitecture of the subchondral bone.[20] Bone remodelling is spatiotemporally orchestrated by local growth factors and cytokines, and the normal subchondral bone is maintained in a naïve microarchitecture with blood vessels and nerves intertwined under normal conditions.[25,26] Disruption of bone remodelling and bone homeostasis inevitably leads to aberrant subchondral bone formation, which induces altered wiring and activity of both nerves and blood vessels in the subchondral bone, subsequently inducing OA pain and the onset and progression of OA.[3,27,28]

Peripheral nerves have critical roles in the physiology and pathology of bone homeostasis.[25,29,30] Both sensory and sympathetic nerve fibres extensively innervate joint tissue, such as the subchondral bone, synovium, and meniscus.[27,31,32] Bone remodelling is also controlled by the nervous system.[18,33-38] Denervation of either peripheral sensory or sympathetic nerves yields massive changes in the bone phenotype.[18,34,39-41] Sites with higher bone remodelling activity are more densely innervated by nerves and vasculature than quiescent sites,[29,38] suggesting a potential role of nerves in regulating subchondral bone remodelling in which bone remodelling activity is increased in the OA subchondral bone. Therefore, it is necessary to comprehensively explore and understand the pathogenesis and pain of OA from the perspective of peripheral nerves, which may subsequently allow the development of effective treatments for OA. In the present review, we focus on the profiles and distribution of sensory and sympathetic nerves in the subchondral bone, the effect of the nerve on OA pain, and the physiology and pathophysiology of subchondral bone homeostasis during OA. Additionally, we also discuss in detail the interaction between bone cells and nerve fibres and the relevant effects of neurotransmitters, cytokines, and factors during OA development.

Nerve distribution and profiles. The knee joint is well innervated by both sensory and sympathetic nerve fibres that have local effects and relay signals between the targeted joint tissue and the central nervous system (CNS).[18,27,31,32,42-46] Sensory neurones from the dorsal root ganglion (DRG) and sympathetic neurones from the sympathetic ganglion disseminate axons to target the subchondral bone and surrounding tissue (Figure 1). The second relay neuron in the spine extends into specific regions of the CNS, such as the brain stem, paraventricular nucleus of the hypothalamus, prelimbic cortex, and motor cortex.[47] The CNS processes the signals collected by sensory nerve endings and subsequently initiates responses to local changes in the environment through dependent or independent sympathetic nerve activity.[45]

In general, nerves enter the epiphysis mainly through the nutrient foramen. The nerve bundles commonly run alongside the arteries that carry nutrition to bone until the formation of free nerve endings or specific structures. Sensory and sympathetic nerve fibres are located near trabecular bone rather than in cortical bone or bone marrow under physiological conditions,[48-51] in which bone remodelling is relatively active. In OA, the densities of both sensory nerve fibres and sympathetic nerves substantially increase in the subchondral bone, especially at sites of increased bone remodelling activity, which is abnormal
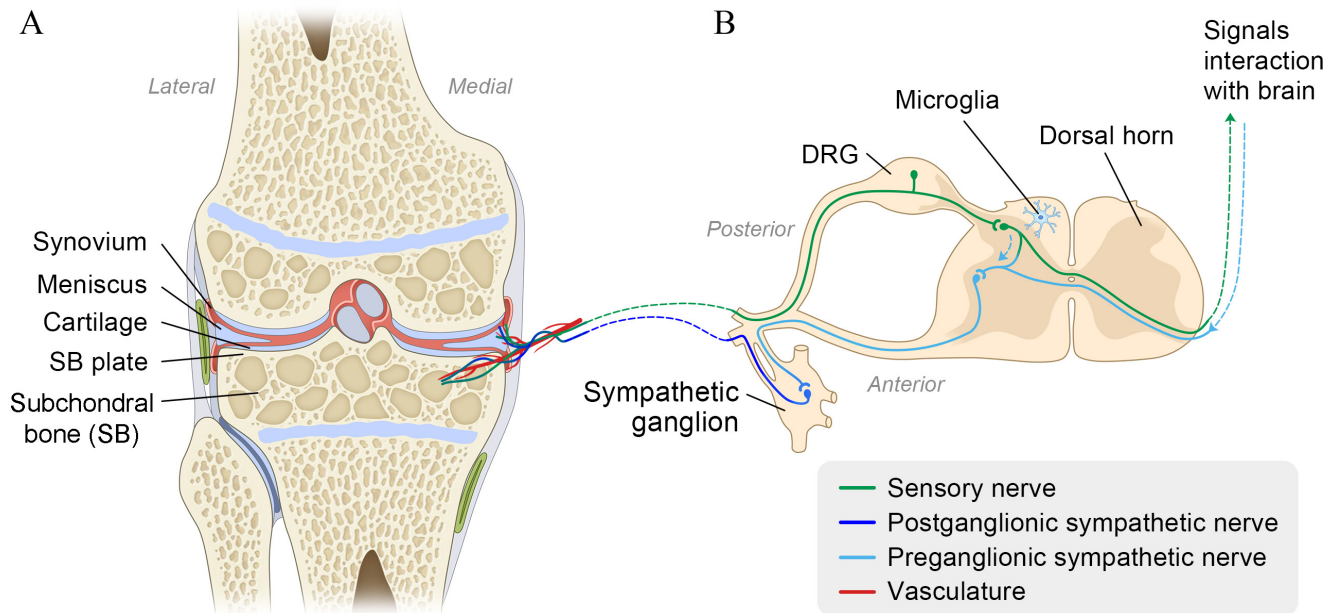
Fig. 1

Peripheral innervation and the route of neuron from central nervous system (CNS) to the knee joint. a) The coronal section of the knee joint; b) the cross-section of the knee-related lumbar spinal cord. The knee joint is well innervated by both sensory and sympathetic nerve fibres with fine nerve branches, including subchondral bone, synovium, and meniscus. Sensory and sympathetic nerves mediate the signals between the joint and CNS after relay in the spinal cord. The sensory nerve has a pseudo-unipolar morphology. The axon derived from dorsal root ganglion (DRG) split into the central branch (forms a synaptic junction with second-order sensory neurones in the dorsal horn to relay the information to CNS) and peripheral branch (extends the target cells or tissues of the joint). After relay in the lateral horn of spinal cord, preganglionic neurone communicates with postganglionic neurone through chemical synapses within the sympathetic ganglion; postganglionic neurone innervated into peripheral target tissues in the joint, commonly accompanied by vasculature (red). Additionally, the sensory nerve can interact with sympathetic nerve at the level of spinal cord.

and uncoupled.[16,27,29,38,46] During the OA process, nerve fibres commonly present an abnormal phenotype, such as aberrant sprouting or a higher expression of neuropeptides.[16,27,28] Osteophytes usually develop at the edges of osteoarthritic joints, especially at the transition site of the articular cartilage and the subchondral bone, into which both nerve fibres and vessels grow. Similarly, the occurrence of osteochondral junctions due to aberrant bone remodelling permits the ingrowth of both nerves and vessels after tidemark penetration. The nerves in the osteophyte and osteochondral junction are continuous with those in the subchondral bone. Abnormal innervation in the whole joint may be responsible for symptom progression and joint pathology in OA. The nerve distribution, neurochemical profile, myelination status, diameter, and electrophysiological properties of the fine nerve branches of the sensory and sympathetic nerve fibres in the subchondral bone are discussed below.

Sensory nerves in the joint. Sensory nerves are a type of neuron that can sense or convert local pain, pressure, and other perceived stimuli into neuronal electrical impulses and conduct sensory information towards the CNS.[52,53] Furthermore, sensory neurones have been shown to generate afferent signals peripherally towards their targets.[52,53] Sensory neurones have pseudounipolar morphology. The axon, which is derived from the soma, splits into the central branch and peripheral branch. The

peripheral branch extends towards the target cells or tissues in the joint. The central branch forms a synaptic junction with second-order sensory neurones to relay information (Figure 1). The peripheral sensory nerves in the knee joint largely originate from neurones in the dorsal DRG alongside the spinal cord at levels 1 to 5 in rodents, mainly from the Lumber 3–5 level DRG.[27,54,55]

Primary sensory nerves are divided into different subgroups and are categorized by axon diameter and conduction velocity, neuropeptide content, myelination status, and distribution.[56,57] To date, Aβ, Aδ, and C sensory fibres have been identified in joints and bone.[25] Most if not all sensory nerve fibres in joints are either thinly myelinated (Aδ) or peptide-rich (C fibres) nerve fibres.[27,44,58-61] Aβ sensory nerve fibres are largely medium myelinated fibres with relatively rapid conduction velocities, and they are mainly related to the detection of stretch, touch, and pressure in joint capsules, despite their absence within the subchondral bone.[25] Both Aδ nerve and C nerve fibres were detected in the subchondral bone.[44,59] Aδ sensory nerve fibres are commonly nonpeptide-rich with occasional free nerve endings, and thinly myelinated fibres primarily transmit signals related to acute pain and mechanical and heat stimuli to the DRG.[25] Compared with Aδ sensory nerve fibres, C nerve fibres are smaller and unmyelinated. They are responsible for the slower onset of deeper pain due to their higher

stimulus threshold,[62] and produce second pain, such as chronic OA pain, that is usually slow, long-lasting, and spread out. C sensory nerve fibres are considered to be responsible for the release of the neuropeptide and substance P in response to various stimuli.[63]

Although sensory nerves showed more extensive distribution near the side of the growth plate in the epiphysis, they also showed good innervation of the subchondral bone (Figures 2a, 2c, and 2e).[64] Only tropomyosin receptor kinase A (TrkA)-, calcitonin gene-related peptide (CGRP)-, and substance P-positive fibres were identified in the subchondral bone; they were either thinly myelinated Aδ fibres or unmyelinated C fibres.[18,19,27,37,44,50,65-67] CGRP+ nerves are the predominant sensory fibres and have varicose-rich ending fibres in the subchondral bone, and they are densely and widely distributed in epiphyseal trabecular bone.[44,49] A retrograde tracing technique showed that approximately 50% of Fast Blue-labelled nerves projecting to the epiphysis in young rats contained CGRP.[55] Notably, CGRP+ and neurofilament 200+ sensory nerves share a similar pattern of distribution, but neurofilament 200+ axons seem to be linear and longer.[44] Compared with CGRP+ nerves, substance P+ nerve fibres are less abundantly innervated in the joint, but they partially coexpress CGRP and form a fine network of varicoses.[44,49,67] Although some studies have failed to detect isolectin-B4 positive peptide-poor C fibres,[44,59] several groups have identified a small number of isolectin-B4+ DRG neural cell bodies innervating the tibia in rats and isolectin-B4+ nerve fibres in the subchondral bone in mice.[27,68] Transient receptor potential cation channel, subfamily V, member 1 (TRPV1)-positive nerve fibres are predominantly unmyelinated sensory fibres and some small-diameter myelinated sensory fibres, and their sensitization contributes to pain hypersensitivity.[69-71] Voltage-gated sodium channel 1.8, which is mainly responsible for detecting noxious stimuli, is preferentially expressed in but not restricted to small-diameter unmyelinated sensory fibres in the subchondral bone.[19,72] Moreover, C sensory fibres with low-threshold mechanoreceptors also express voltage-gated sodium channel 1.8 for touch sensation.[72] In OA, the sensory nerves in the subchondral bone present dramatic alterations in distribution, density, and activity.[27,28] For example, osteoclast activity and number increase, leading to abnormal sensory innervation and subsequent OA pain.[27,28] Specifically, aberrant subchondral remodelling induced by osteoclasts promotes an increased number of CGPR+ sensory nerves,[28] and the expression of voltage-gated sodium 1.8 in the sensory nerve increases and synergistically induces OA pain with stimulation of PGE2 synthesis.[27]

Sympathetic nerves in the joint. The autonomic nervous system, which consists of the sympathetic nervous system and parasympathetic nervous system, coordinates functions throughout the whole body to ensure homeostasis through adaptive responses to various stresses. Both the sympathetic nervous system and parasympathetic nervous system project their small, unmyelinated axons with a relatively slow velocity of conduction to target tissues. Preganglionic neurones communicate with postganglionic neurones through chemical synapses within an autonomic ganglion (Figure 1). Generally, upon stimulation by acetylcholine derived from preganglionic neurones, postganglionic neurones principally release factors, such as norepinephrine (NE), to peripheral tissue to mediate autonomic outflow.

Currently, the distribution of sympathetic nerves in the subchondral bone in mammals is not well pictured. Sympathetic nerves in the bone marrow are primarily thought to be vasomotor nerves due to their perivascular arrangement (Figures 2a, 2c, and 2e), but they dissociate from the vasculature to form free nerve endings in the bone marrow.[67,73] Sympathetic nerve fibres are abundant in the skeleton and are commonly identified by their immunoreactivity to tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis.[2,44,74] Additionally, dopamine β-hydroxylase, monoamine oxidase, and catechol-O-methyltransferase also often colocalize with sympathetic nerves because of their participation in the synthesis of NE in sympathetic neurones.[74] The majority of neuropeptide Y (NPY) is also largely colocalized and coreleased with NE in sympathetic nerves; NPY+ nerve fibres are confined to the vasculature and occasionally have close contact with bone lining cells.[49] Postganglionic sympathetic neurones have been demonstrated to have a cholinergic neurochemical profile in bone and joints.[75,76] Nerve fibres containing vasoactive intestinal polypeptides (VIPs) have also been identified in bone marrow.[2,49,75] Abolition of VIP staining in bone after sympathectomy suggests that VIP+ nerve fibres are largely derived from the sympathetic nervous system.[77] The literature about alterations of sympathetic nerves is sparse. NPY+ sympathetic nerve fibres were detected at the base of the subchondral bone and tibial osteophytes,[16] suggesting that NPY is involved in controlling bone metabolism in the subchondral bone and is related to the formation of osteophytes. The sympathetic nerves primarily present their perivascular arrangement, the volume of blood vessels increases, and sympathetic nerve distribution appears to change with abnormal subchondral bone remodelling in OA.[3] A similar alteration of sympathetic nerves in the subchondral bone is expected.

The role of the nervous system in OA pain. Patho physiological OA pain is a severe manifestation of OA; it is induced mainly by the aberrant function of the pathologically altered nervous system. Neurochemical and structural changes in sensory nerve fibres and alterations in the CNS are the major sources of chronic OA pain. The sensitization and dysregulation of the CNS are not our key points in this review, so we will not discuss them in detail. Chronic OA pain, including hypersensitivity, hyperalgesia (exaggerated pain response to noxious stimuli), and allodynia (innocuous stimuli are perceived as painful), is induced by abnormal nociceptive input and peripheral sensitization in the OA subchondral bone.
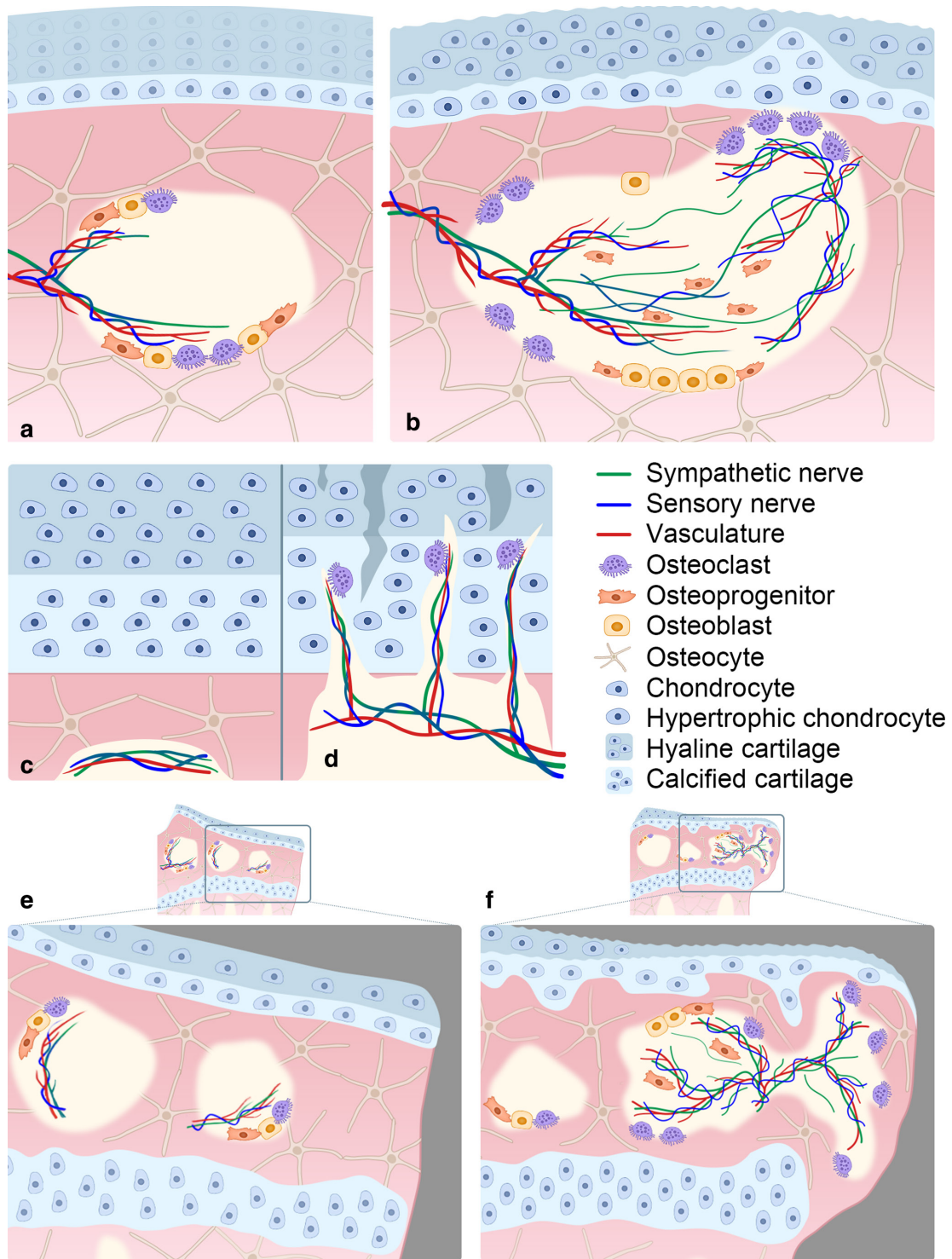
Fig. 2

The physiological and pathological distribution of peripheral innervation in the subchondral bone. a) and b) Schematic distribution and patterning of peripheral nerves in a) normal subchondral bone and b) osteoarthritis (OA) subchondral bone. Sensory and sympathetic nerves with vasculature present a fine branching in the subchondral bone. Both mainly locate near subchondral bone surfaces and near the bone cells, such as osteoblasts, osteoprogenitors, and osteoclasts. In OA, coupled with increased bone turnover and abnormal recruitment of osteoprogenitors, both sensory and sympathetic nerves showed aberrant and abnormal distribution, such as increased intensity and abnormal sprouting. c) and d) Peripheral innervation within osteochondral junction in c) normal and d) OA condition. Sensory nerves, sympathetic nerves, and vasculature remain in the subchondral bone without invasion into cartilage under normal conditions. In OA, the sensory and sympathetic nerves, coupled with vasculature enter calcified cartilage (CC) and even hyaline cartilage from aberrant subchondral bone through the osteochondral channels that may be induced by overactive osteoclast activity. e) and f) Peripheral innervation in e) normal subchondral bone and f) osteophytes. Sensory and sympathetic nerves with vasculature present a fine branching in the normal subchondral bone. In OA, the sensory and sympathetic nerves, accompanied by vasculature, enter into osteophytes from aberrant subchondral bone, coupled with overactive osteoclast activity.

The sensory innervation in the OA subchondral bone is fundamental to peripheral sensation and nociception. Removal of the subchondral bone and articular cartilage allows OA patients to have obvious pain relief in TKA,[10,11] which indicates the important role of the subchondral bone in OA pain. Soluble blockade of NGF effectively suppresses OA pain in both the early and late stages,[78] whereas inhibition of inflammatory factors or cellular infiltration into the joint only suppresses OA pain in the early stages, suggesting that OA pain, especially in later stages, is primarily derived from noninflammatory aspects.[79] During OA progression, channels across the osteochondral junction are formed that permit vessel and nerve fibres to cross the tidemark into articular cartilage or osteophytes. This is a result of aberrant subchondral bone microarchitecture due to abnormal bone remodelling, and the nerves are derived from nerves in the subchondral bone (Figure 2).[16,80,81] Therefore, OA pain can also originate from the osteochondral junction and osteophytes in the OA joint (Figures 2d and 2f). In contrast to the production of antiangiogenic factors by chondrocytes in healthy cartilage, both the subchondral bone and the hypertrophic chondrocytes in the OA joint produce NGF and proangiogenic factors, such as vascular endothelial growth factor (VEGF), to promote angiogenesis and subsequent innervation.[80,82] Indeed, nerves and vasculatures share similar wiring mechanisms that facilitate their interplay.[83] Perivascular nerve growth in osteophytes, osteochondral junctions, and articular cartilage may be abnormal; due to their exposure, these nerve fibres are easily stimulated by chemical and mechanical stress. Therefore, neovascularization and accompanying sensory innervation in the osteochondral junction and osteophyte contribute to OA pain.

A potential mechanism of OA pain is the pathological sprouting and structure of sensory nerve fibres in the subchondral bone (Figures 2b, 2d, and 2f). The altered concentration or distribution of axonal guidance molecules in the subchondral bone leads to aberrant sensory innervation and OA pain. A recent study revealed that elevated netrin-1 promotes the growth of CGRP+ sensory nerves in aberrant subchondral bone, and specific knockout of netrin-1 from osteoclasts dramatically attenuates pain hypersensitivity by reducing sensory innervation,[27] suggesting that abnormal sensory nerve sprouting in the subchondral bone induces OA pain. Whether alterations in other guidance cues, such as SLITs, semaphorins, and ephrins, are involved in OA pain remains unclear. Moreover, increased resorption of bone matrix by elevated osteoclast activity leads to greatly increased local calcium levels, which further contribute to aberrant nerve growth by binding to the calcium-sensing receptor of sensory nerves[84] and inducing abnormal signal conduction from sensory nerve terminals to the CNS. Additionally, the density of sensory nerve fibres was reported to be increased approximately ten- to 70-fold in the bone marrow of a bone prostate cancer model, and blockade of pathological sprouting of sensory nerve fibres and

neuroma formation by NGF reduced the generation of pain.[78] Inappropriate sprouting or neuroma formation in skeletal tissue,[19,27,78] including the endplate or subchondral bone, contributes to hypersensitivity to innocuous stimuli and movement-evoked pain. Exuberant nerve sprouting has been suggested to be a major cause of pathological OA pain.

The sensitization and neuropathic degeneration of peripheral sensory nerves are also critical to OA pain. The expression of voltage-gated sodium 1.8 on sensory nerves in both the subchondral bone and the endplate was reported to markedly increase with increased PGE2 after lumbar spine instability,[19,28] which is correlated with hypersensitivity and abnormal pain behaviour. The pain of bone cancer metastases, such as prostate sarcoma and breast sarcoma, shows that the tumour appears to closely contact and subsequently injure sensory nerve fibre endings,[85] which leads to neuropathic pain. Certain types of bone pain are attenuated by gabapentin,[86] which is an approved treatment for neuropathic pain, suggesting that injured sensory neurones lead to bone pain.[87,88] The destruction of sensory nerve fibres at the injured site is correlated with increased movement-evoked pain behaviour,[85] and a similar pattern of pain implicates nerve fibre damage in the OA joint caused by microcracks in the subchondral bone or overactive osteoclast activity. The above evidence suggests that neuropathic pain is one of the origins of OA pain.

Several factors, including PGE2 and NGF, are involved in the regulation of OA pain by interacting with sensory nerves (Figure 3a).

PGE2 contributes to altered neuronal excitability. PGE2 has been indicated to contribute to persistent neuropathic pain and promote the expression of pain-related molecules, including CGRP and substance P, in sensory neurones.[89] Increased PGE2 facilitates the trafficking of voltage-gated sodium 1.8 to the surfaces of neurones and mediates pain transduction in sensory neurones, which further induces hypersensitivity to OA pain.[28] Moreover, protein kinase A induced by PGE2/prostaglandin EP4 receptor (EP4) signalling activates multiple molecules, including voltage-gated calcium or sodium channels, TRPV1, and purinergic P2X3 receptors, in nociceptors, leading to hyperalgesia. Therefore, inhibiting PGE2 signalling (e.g. by applying non-steroidal anti-inflammatory drugs) supports pain relief by inhibiting both nerve stimulation and inflammation.

Aberrant expression of NGF is also highly correlated with OA pain. NGF produced by osteochondral blood vessels promotes ingrowth of nociceptive nerves into osteochondral junctions in OA.[80] In arthritis disease, NGF induces stimulation of PGE2 synthesis, which indirectly leads to hyperalgesia.[90] Overexpression of NGF in peripheral tissue with damage, such as deteriorated subchondral bone, leads to upregulated expression of pain-related molecules,[91] such as CGRP, substance P, and TRPV1, and nociceptive ion channels, such as voltage-gated sodium 1.8. Additionally, NGF indirectly leads to hyperalgesia
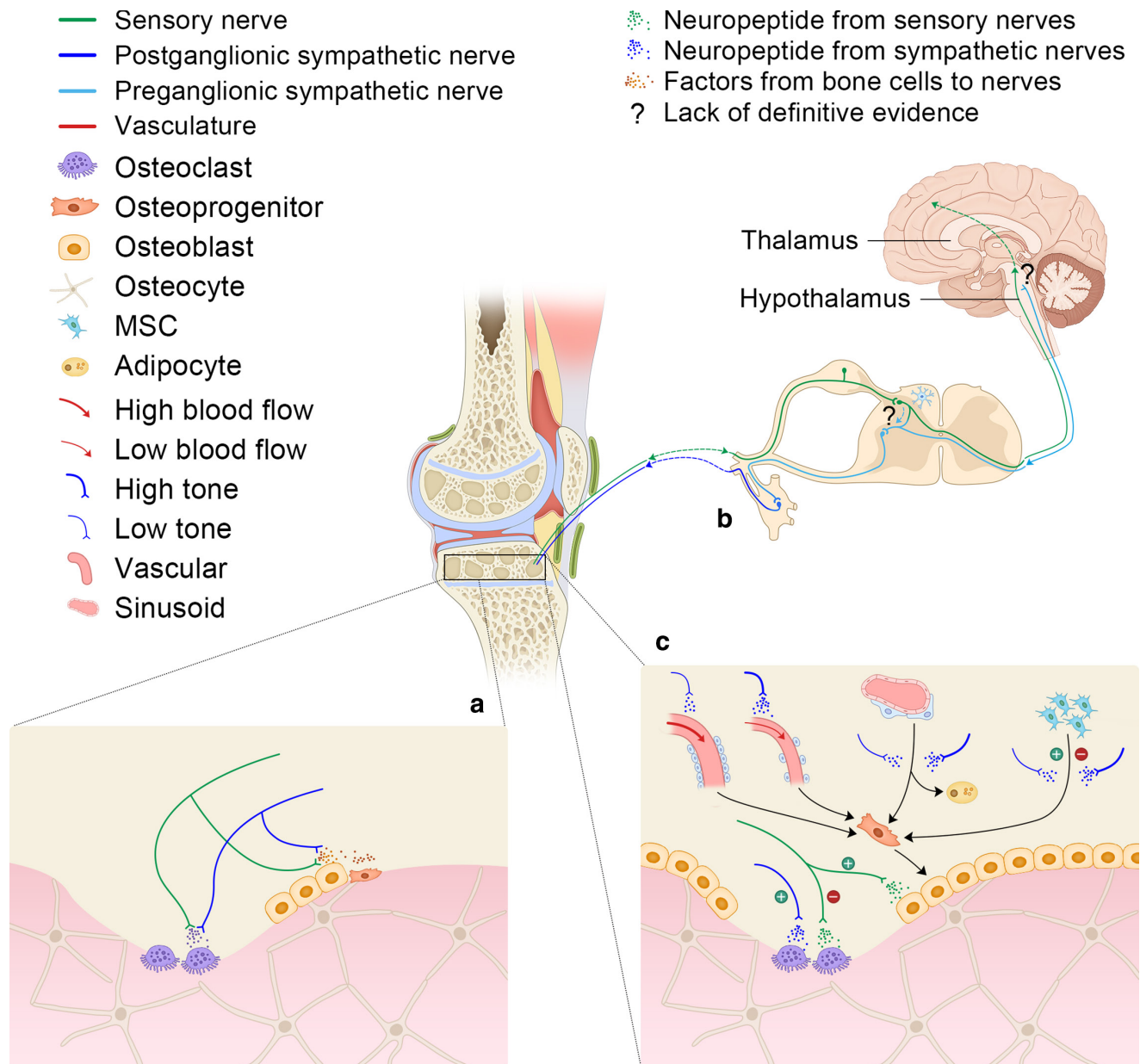
Fig. 3

The schematic of regulation of peripheral nerves in subchondral bone homeostasis and pain sensation. a) The local factors and molecules from resident cells, including osteoblast, osteoclast, and osteoprogenitors or other cells, activate sensory nerves, and then they mediate both metabolic and pain signals to central nervous system; local factors, such as netrin-1 and SLIT3, also affect both sensory nerve and sympathetic nerve by guiding their ingrowth. b) Sensory nerves collect and transport signals of peripheral tissue to brain after second-relay in the spinal cord. The pain signals are projected to brain cortex while sensory nerve mediates metabolic signals and turns down the tone of sympathetic signals at hypothalamus and spinal levels. c) Sympathetic tone regulates bone remodelling both directly and indirectly. Reduced sympathetic tone that is dependent or independent of sensory activity may promote proliferation of osteoprogenitors via increase of blood flow and subsequently increased generation of type H vessel. Reduced sympathetic tone also promotes mesenchymal stem cells (MSCs) to differentiate into adipocyte and directly promote the proliferation and differentiation of osteoblast lineage cells. Sympathetic molecules including neuropeptide Y and vasoactive intestinal polypeptide promote osteoclastogenesis, and inhibit the activity and differentiation of osteoblast lineage cells. The sensory molecules, such as calcitonin gene-related peptide and substance p, have a dual role in the inhibition of osteoclast activity and promotion of osteoblast lineage cells.

through its effects on other cells. NGF/TrkA signalling triggers the release of pain mediators in mast cells and promotes angiogenesis and nerve growth.[80,92] NGF also enhances the process of nociceptive signal transmission from sensory nerves to the CNS through direct activation of TrkA or indirect mechanisms,[93] as verified by reduced OA pain after specific inhibition of NGF.[6] A randomized controlled trial (RCT) demonstrated that blockade of NGF yielded a significant reduction in walking knee pain and improved function for up to eight weeks.[94]

The metabolic effects of nerves in the joint. The nervous system plays an important role in the control of bone

homeostasis by directly or indirectly affecting a variety of different skeletal cells or their interaction (Figure 3). Both chemical and surgical denervation result in bone loss in both loaded and unloaded bones.[39,40] Briefly, peripheral nervous systems regulate bone metabolism through two pathways: 1) trophic factors derived from nerves directly affect both the functionality and structure of bone; and 2) nerves coordinate bone homeostasis through the collection of local signals ascending to the CNS and by amplifying signals descending from the CNS.[95]

Central control of bone homeostasis, composed of central neuronal pathways and neurotransmitters, mainly targets osteoblasts and osteoclasts, and possibly osteocytes, to regulate the equilibrium between bone formation and resorption.[89] In addition, the energy metabolism regulated by the CNS partially affects bone mass, which is a part of the central control of bone homeostasis. Central regulators of bone metabolism, such as leptin, have been identified which centrally control bone mass by regulating the differentiation, proliferation, and function of osteoclasts and osteoblasts.[89]

Peripheral nerve fibres are closely involved in bone remodelling in direct and indirect ways (Figures 3a to 3c). Generally, areas of bone that receive higher mechanical stress commonly exhibit higher bone turnover and metabolic rates. Sites of bone remodelling are also commonly accompanied by abundant vascular and peripheral nerve innervation, including sympathetic and sensory fibres.[38]

Sensory nerve fibres were observed at innervated sites of incipient primary ossification, coincident with NGF expression in cells adjacent to centres of incipient ossification (Figure 3a).[96] Innervation of TrkA+ nerve fibres into the fracture site precedes angiogenesis, and chemical denervation attenuates bone formation.[37] These results indicate that nerves sustain bone homeostasis by locating adjacent bone surfaces in developmental and repair conditions. In response to low bone density, mechanical stress, or fracture healing, sensory nerves promote bone formation, and the blockade of EP4 activation or NGF/TrkA signalling in sensory nerves dramatically attenuates bone formation.[18,37,38] Sensory denervation has also been demonstrated to result in reduced bone mineral density (BMD), especially for trabecular bone, which is related to the increased/decreased activity and number of osteoclasts/osteoblasts.[97,98] The increased density of sensory nerves in the subchondral bone favours osteoblast differentiation and suppresses osteoclastogenesis to shift bone homeostasis towards bone formation in OA. Furthermore, the aberrant sprouting of sensory nerves also disturbs bone remodelling due to its abnormal distribution and activity.

The effect of neuropeptides derived from sensory nerves on bone cells. CGRP, an important osteoanabolic peptide, can increase proliferation, promote osteogenic differentiation and the expression of osteoblastic genes, and reduce apoptosis of osteoprogenitor cells in vitro.[99,100] In general, CGRP has a direct effect on osteoblasts by regulating their cellular activity; CGRP enhances osteogenesis by increasing the production of cyclic adenosine monophosphate and the subsequent activation of protein kinase A (PKA)/cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB) and Wnt/β-catenin in osteoblasts.[101-103] Additionally, implant-derived magnesium has been shown to improve bone healing via locally increased production of CGRP in rats.[104] Transgenic mice lacking CGRP exhibited decreased bone formation and reduced trabecular bone mass, but cortical bone was unaffected.[105] Decreased bone formation and osteopenia were observed in mice lacking alpha-calcitonin gene-related peptide. It has been proven that nerves containing CGRP have an inhibitory effect on osteoclastic bone resorption.[106] Characterization of immunoreactive CGRP produced by a CGRP receptor-positive cloned osteosarcoma cell line showed that CGRP directly inhibits osteoclast maturation and activity, and indirectly modulates osteoclastogenesis by regulating the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG).[98,100]

Substance P is largely coexpressed and coreleased with CGRP in sensory nerves, suggesting its overlapping role with CGRP in several physiological and pathophysiological processes.[107] The effect of substance P on osteoblast osteoprogenitor cells remains controversial; both inhibition and enhancement of mineralized bone formation have been reported.[108,109] In contrast to its undefined effect on osteoblasts, substance P promotes osteoclastogenesis and stimulates subsequent resorption through direct or indirect upregulation of RANKL.[110-112] Local osteolysis leads to increased osteoclast activity and decreases bone volume, which is substantially reduced in substance P-deficient mice.[113] The literature about the pathological effect of substance P in OA is sparse. In the OA femoral head, the density of substance P+ nerve fibres in trabecular bone was increased in line with pain intensity and deterioration of bone structure,[114] indicating the negative role of substance P in the preservation of the bone structure of the OA joint. Substance P may affect subchondral bone remodelling through its effect on osteoblasts and osteoclasts. The exact mechanism needs to be further elucidated. Inhibition of substance P may attenuate deterioration of the subchondral bone via inhibition of overactive osteoclasts and related aberrant bone remodelling.

Sympathetic nerves in the regulation of bone homeostasis. The sympathetic nervous system is the predominant efferent pathway from the CNS controlling skeletal metabolism (Figures 3b, 3c, and 4).[33,34] Chemically or surgically induced activation of sympathetic activity leads to bone loss, and blockade of sympathetic tone promotes bone formation.[34,41] Reflex sympathetic dystrophy, characterized by high sympathetic tone, also leads to low bone mass in humans.[115] Chronic stress-induced sympathetic activity shifts bone homeostasis to bone resorption, as verified by enhanced bone resorption in mice after chronic stimulation with a low-dose agonist of beta adrenergic receptors (βARs).[33]
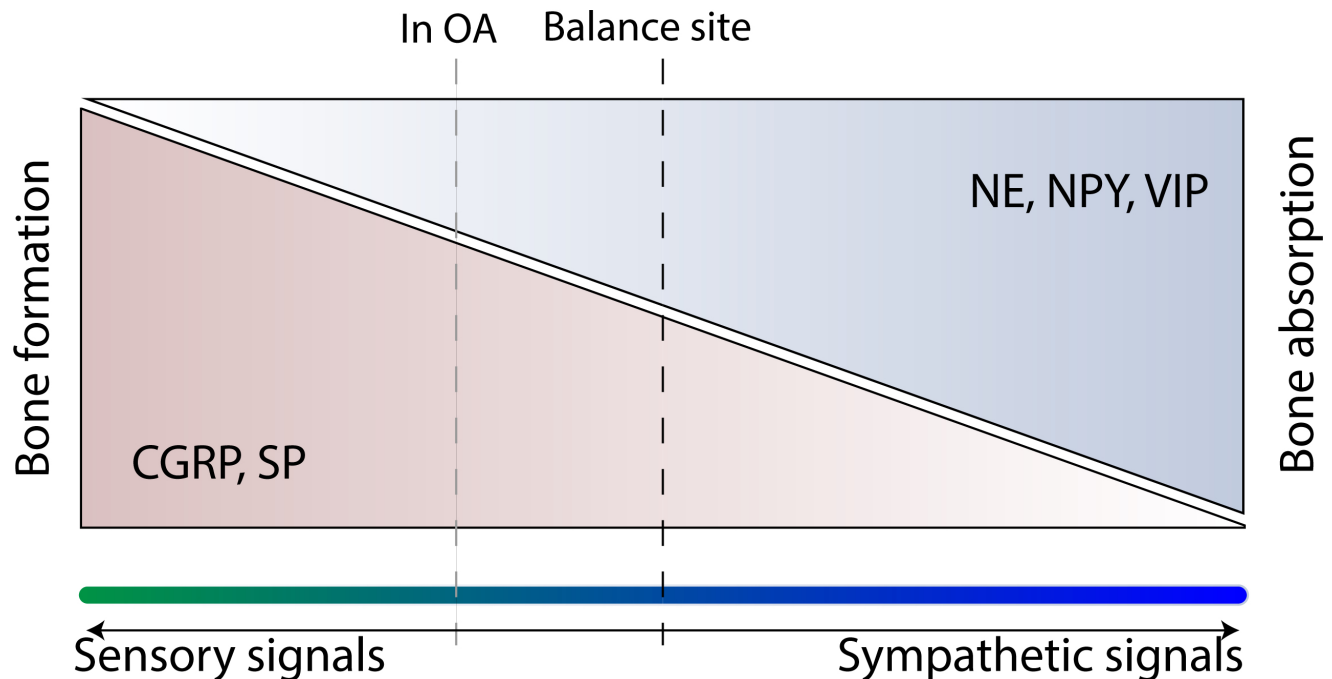
Fig. 4

The homeostasis of subchondral bone under the control of the nervous system. The homeostasis of subchondral bone is regulated by peripheral sensory and sympathetic signals. The higher sympathetic tone has a tendency of bone resorption, commonly coupled with increased production of neuropeptide such as norepinephrine (NE), neuropeptide Y (NPY), and vasoactiveintestinal polypeptide (VIP). In contrast, activation of sensory nerves leads to bone formation with production of neuropeptide, such as calcitonin gene-related peptide (CGRP) and substance P (SP). In normal conditions, the intensity between sensory signals and sympathetic signals are maintained in balance (the normal condition, black dash line). In osteoarthritis (OA), the balance is disrupted, and predominance of signals shifts from higher sympathetic nerve to sensory nerve during OA progression, coupled with deterioration of subchondral bone and OA pain. At the end stage, the abnormal balance emerges (the condition that sensory signals exceed the sympathetic signals, grey dash line), consistent with increased bone volume of subchondral bone.

In both trabecular bone and cortical bone, the majority of the sympathetic nerves were morphologically observed to be closely associated with vascular structures, mainly including large arteries, small arteries, or capillaries, which are essential to skeletal growth, development, and repair.[29,97,116-118] We assume that sympathetic nerves partially affect bone metabolism by controlling vessel activity. The colocalization of unmyelinated tyrosine hydroxylase+ sympathetic nerve fibres and arterioles permits sympathetic nerve activity to control blood flow in the limb.[116,119] Blood flow controls Type H vessels that couple angiogenesis and osteogenesis by regulating Notch signalling.[120] Accordingly, sympathetic nerves, specifically those with higher sympathetic tone, affect bone homeostasis by decreasing blood flow and subsequently decreasing the formation of type H vessels in OA. In a temporomandibular joint OA model, OA rats showed robust sprouting of tyrosine hydroxylase (TH) positive nerve fibres and increased NE levels in the subchondral bone compared to control rats.[121] Elevated sympathetic nervous activity leads to bone loss, especially in trabecular bone, by increasing bone resorption and inhibiting bone formation, and blockade of βARs greatly attenuates bone loss.[122,123] In addition, neuropeptides from sympathetic nerves are directly involved in bone homeostasis.

NE, a canonical neurotransmitter of peripheral sympathetic nerves, elicits sympathetic nerve function through adrenergic receptors (ARs). ARs include three subtypes, the β (cAMP stimulation), α1 (phospholipase C stimulation), and α2 (cAMP inhibition) subtypes, based on their downstream messengers. Activation of βAR contributes to increased osteoclast formation and bone loss, as evidenced by nonselective β1AR and β2AR agonist-stimulated osteoclastogenesis in rats and mice.[34] βAR stimulation also affects bone formation by inhibiting osteoblast proliferation, blockade of βAR stimulates osteoblast proliferation, and activation of βAR inhibits osteoblast proliferation. Furthermore, osteoblast β2AR-deficient mice have higher bone mass,[34,124,125] confirming that sympathetic signals regulate bone remodelling via β2AR on osteoblasts.

NPY is involved in the control of osteoblast activity and subsequent bone formation.[126] Leptin signals via NPY+ neurons to coordinate energy partitioning between the bone mass and fat,[127] and deletion of NPY leads to increased bone formation. Application of NPY to the hypothalamus effectively recapitulates bone loss, suggesting an essential role of NPY in bone metabolism and the central regulation of the hypothalamus in bone remodelling.[128] Hypothalamus-specific deletion of

Y2R promotes osteoblast activity, thus increasing both trabecular and cortical bone formation.[129] The decreased expression of NPY in primary calvarial cultures after shear stress leads to increased markers of osteoblast differentiation, highlighting the negative regulatory effect of NPY on the differentiation of osteoblast lineage cells.[130] Upon activation of Y1 in osteoblast lineage cells, NPY locally inhibits the differentiation of mesenchymal progenitors and mineral production by mature osteoblasts.[130,131] NPY+ sympathetic nerve fibres were detected at the base of the subchondral bone and tibial osteophytes,[16] suggesting that NPY is involved in controlling the bone metabolism of the subchondral bone and is related to the formation of osteophytes.

VIP plays roles in regulating bone cells via its receptors on osteoblasts and osteoclasts in humans and mice.[48] Regarding osteoblasts, VIP was found to promote osteoblast activity by inducing alkaline phosphatase (ALP) gene expression via a cAMP response.[132] VIP also inhibits transforming growth factor (TGF) β1 production in murine macrophages,[133] and inhibition of excessive TGF-β1 in the subchondral bone is beneficial for OA progression.[3] VIP shows a tendency to inhibit bone resorption.[134] The protective effects of VIP against collagen-induced arthritis are indicated by delayed onset of OA and dramatically reduced subchondral bone and cartilage degeneration.[135]

Interaction between sympathetic and sensory innervation. The similar bone phenotypes observed in sympathetic hyperfunction and sensory denervation indicate the possibility of functional interaction between the sensory nerve and sympathetic nervous system in the control of bone metabolism or independent function of bone metabolism in an opposing manner.[89] The evidence supports the former hypothesis (Figure 3). The activation of sensory nerves in bone has also been reported to inhibit sympathetic nervous system tone through the hypothalamus to control homeostasis.[18] Additionally, attenuated bone loss and activation of sensory nerves with increased expression of CGRP were observed after the application of β-blockers in hypertensive rats or after chemical sympathectomy.[136,137] A portion of sensory nerves extending from the DRG is located on the surface of the bone to sense biomechanical signals or other microenvironmental changes.[38] Recent studies have suggested that osteoblasts serve as sensors of mechanical or chemical stimuli and transmit these signals to the CNS via sensory nerves.[18,37,38,138] Other bone surface cells may also have roles as sensors. The authors postulated that low bone volume or low BMD is sensed by osteoblasts, possibly due to altered mechanical stress, thus upregulating the expression of PGE2. The PGE2-EP4 sensory nerve axis regulates mesenchymal stromal cell lineage commitment in the bone marrow of adult mice through regulation of sympathetic tones.[139] Therefore, disrupted remodelling of the subchondral bone leads to aberrant sensory and sympathetic innervation in OA, which conversely has a negative effect on subchondral bone homeostasis.

PGE2 induces the dilation of vessels and inhibits the release of NE from sympathetic neurones.[140] Exogenous PGE2 has the ability to stimulate both bone formation and resorption via the production of cAMP in bone,[141] but the direct effects of endogenous PGE2 on osteoblasts and osteoclasts in vivo are still being defined. Knockout of cyclooxygenase-2 in mice results in increased serum markers of bone resorption, decreased femoral BMD, and decreased thickness of cortical bone and trabecular bone.[141] Therefore, partial inhibition of PGE2 reduces OA pain while maintaining the normal effect of PGE2 on subchondral bone remodelling.

Factors derived from bone cells in the regulation of peripheral nerve growth and wiring. Cell-derived factors play a critical role in the growth and wiring of peripheral nerves by diffusing to target receptors on nerves. Several vital molecules, including NGF, netrin-1, and semaphorin 3A, modulate bone remodelling indirectly by regulating the nervous system in an autocrine manner.

NGF is a well-known neurotrophic molecule. The phosphorylation of TrkA by NGF at axon tips initiates diverse signals for metabolic regulation. NGF/TrkA signalling supports the survival and development of neurones; the NGF/TrkA complex undergoes retrograde transport from axon terminals to the cell body.[142,143] NGF expression in osteoblasts markedly increased in response to mechanical loading, and the activation of TrkA+ sensory nerves induced increased bone formation, load-induced bone formation, and Wnt/β-catenin activity in osteocytes,[38] indicating that osteoblasts are required for skeletal adaptation to mechanical loads. TrkA+ sensory nerves are projected from the DRG to the surfaces of newly forming bone, where NGF is highly expressed.[96] Mutant TrkA mice present attenuated bone formation after mechanical loading,[38] and blockade of NGF/TrkA signalling attenuates nerve sprouting,[144] indicating that sensory nerves are vital for the effects of NGF on bone formation.

Netrin-1 is an axon guidance molecule that can function as an attractant or repellent, respectively, through its receptor. Highly expressed in osteoblasts and osteoclasts,[27,145] it has been shown to prevent bone destruction in ageing animals and bone erosion in autoimmune arthritis via inhibition of osteoclast maturation.[145] Osteoclast-derived netrin-1 has also been shown to induce sensory nerve innervation of the subchondral bone in a surgery-induced OA mice model.[27] Overexpression of netrin-1 promotes functional recovery from peripheral nerve injury in bone marrow stromal cells, indicating its potential application as a treatment for nerve injury.[146] Netrin-1 plays a positive role in promoting peripheral nerve regeneration.[147]

Semaphorin 3A, a well-known diffusible axonal repellent, is ubiquitously expressed in a variety of tissues and abundantly expressed in bone. Semaphorin 3A deficiency contributes to bone and cartilage abnormalities due to abnormal innervation.[148,149] Furthermore, neuron-specific deletion of semaphorin 3A led to decreased bone formation and low bone mass, while osteoblast-specific

semaphorin 3A-deficient mice did not display any bone abnormalities, despite a substantial decrease in semaphorin 3A in bone.[149] Semaphorin 3A signalling spatiotemporally precedes or coincides with the invasion of blood vessels and nerve fibres in bone.[150]

Perspectives on clinical translation. Articular cartilage degeneration is considered to be the primary concern and lead cause of OA. However, it is not sufficient to attenuate disease progression solely through protection of the articular cartilage.[3] Despite the current lack of abundant clinical evidence, treatment targeting the signalling mechanisms responsible for the regeneration, survival, and signal transduction of peripheral nerve in the joint may be an alternative for halting OA progression.

Denervation or inhibition of sensory innervation not only contributes to pain control, but also reduces joint degeneration. Clinical trials have illustrated that an anti-NGF antibody, fulranumab and tanezumab, showed a substantial improvement in physical pain and joint function scores.[151–154] This indicates that regulation of the peripheral nervous system might help to combat OA. Whether antibodies that can neutralize other nerve factors or nerve-guiding factors, such as netrin-1, semaphorin 3A, and SLIT3, have a beneficial effect on OA in humans, as well as the doses at which they would be effective, remains unclear. Furthermore, topical application of capsaicin that can reduce sensory innervation effectively has been shown to reduce OA pain of the knee, hand, shoulder, or hip.[155] However, the protective effect of capsaicin on OA progression is limited. The physical density of sensory nerve is responsible for subchondral bone homeostasis. Therefore, lower doses of capsaicin may have a better efficacy of OA improvement.

Attenuation of sympathetic tone has been demonstrated to increase bone volume.[18,19] Proper local activation of sympathetic tone may help slow down the sclerosis of subchondral bone. Electrical stimulation or acupuncture specifically on degenerated joint has a potentially beneficial effect on OA. The detailed intensity or method and the effect need further exploration.

Interrupting signal transduction of nerve is a good choice of pain control. Inhibition of the chemokine (C-C motif) ligand 2 (CCL2)-CC chemokine receptor 2 (CCR2) and PGE2/EP4 signalling axes ameliorates OA pain,[156,157] and drugs or molecules, such as celecoxib, targeting the signalling pathway may be a therapy for OA. Low dose of celecoxib reduces vertebral endplate porosity and spinal pain via skeleton interoception activity.[156] Therefore, low dose of celecoxib may have a better effect on OA than a normal dose, although there is a lack of clinical evidence supporting this.

In conclusion, both sensory and sympathetic nerve fibres play important roles in subchondral bone remodelling and OA pain through their neurotransmitters, neuropeptides, and their interactions in OA. Evidence of the impact of peripheral nerves on OA progression and pain is emerging but remains inadequate. Various resident cells in the subchondral bone have receptors for sensory and sympathetic neurotransmitters and neuropeptides, such as CGRP and NE, which allow osteoblasts, osteoclasts, or endothelial cells to respond to neuronal stimuli. Bone cells also affect nerve fibres through factors or molecules, such as PGE2, netrin-1, and NGF, to modulate nerve wiring and hypersensitivity. Uncoupled subchondral bone remodelling induces OA and leads to disordered nerve distribution and activity in OA. Conversely, abnormal nerve innervation in the subchondral bone may lead to aberrant subchondral bone remodelling via local or central regulation of osteoblasts and osteoclasts and potentially blood vessels, thus forming a vicious circle. Prevention of abnormal nerve wiring and activity may be beneficial to subchondral bone structure and OA pain. Drugs targeting aberrant peripheral innervation or local factors, perhaps in only specific subpopulations, contribute to pain control and prevent joint degeneration in OA. Despite the current lack of validation and application in the clinic, studies focusing on the peripheral nerves in OA can potentially provide alternatives for OA therapy by alleviating OA pain and attenuating OA progression.

References

1. **Hootman JM**, **Helmick CG**. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis Rheum*. 2006;54(1):226–229.
2. **Murray CJL**, **Vos T**, **Lozano R**, **et al**. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197–2223.
3. **Zhen G**, **Wen C**, **Jia X**, **et al**. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. *Nat Med*. 2013;19(6):704–712.
4. **Pereira D**, **Peleteiro B**, **Araújo J**, **Branco J**, **Santos RA**, **Ramos E**. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. *Osteoarthr Cartil*. 2011;19(11):1270–1285.
5. **Zhao HY**, **Yeersheng R**, **Kang XW**, **Xia YY**, **Kang PD**, **Wang WJ**. The effect of tourniquet uses on total blood loss, early function, and pain after primary total knee arthroplasty: a prospective, randomized controlled trial. *Bone Joint Res*. 2020;9(6):322–332.
6. **Lane NE**, **Schnitzer TJ**, **Birbara CA**, **et al**. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010;363(16):1521–1531.
7. **Malfait AM**, **Schnitzer TJ**. Towards a mechanism-based approach to pain management in osteoarthritis. *Nat Rev Rheumatol*. 2013;9(11):654–664.
8. **Mathiessen A**, **Conaghan PG**. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther*. 2017;19(1):18.
9. **Eitner A**, **Wildemann B**. Diabetes - osteoarthritis and joint pain. *Bone Joint Res*. 2021;10(5):307–309.
10. **Isaac D**, **Falode T**, **Liu P**, **I'Anson H**, **Dillow K**, **Gill P**. Accelerated rehabilitation after total knee replacement. *Knee*. 2005;12(5):346–350.
11. **Reilly KA**, **Beard DJ**, **Barker KL**, **Dodd CAF**, **Price AJ**, **Murray DW**. Efficacy of an accelerated recovery protocol for Oxford unicompartmental knee arthroplasty--a randomised controlled trial. *Knee*. 2005;12(5):351–357.
12. **Bhosale AM**, **Richardson JB**. Articular cartilage: structure, injuries and review of management. *Br Med Bull*. 2008;87(1):77–95.
13. **Yusuf E**, **Kortekaas MC**, **Watt I**, **Huizinga TWJ**, **Kloppenburg M**. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. 2011;70(1):60–67.
14. **Kwoh CK**. Clinical relevance of bone marrow lesions in OA. *Nat Rev Rheumatol*. 2013;9(1):7–8.
15. **Laslett LL**, **Doré DA**, **Quinn SJ**, **et al**. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Ann Rheum Dis*. 2012;71(8):1322–1328.
16. **Suri S**, **Gill SE**, **Massena de Camin S**, **Wilson D**, **McWilliams DF**, **Walsh DA**. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Ann Rheum Dis*. 2007;66(11):1423–1428.
17. **Kan S-L**, **Li Y**, **Ning G-Z**, **et al**. Tanezumab for patients with osteoarthritis of the knee: a meta-analysis. *PLoS One*. 2016;11(6):e0157105.

18. **Chen H**, **Hu B**, **Lv X**, **et al**. Prostaglandin E2 mediates sensory nerve regulation of bone homeostasis. *Nat Commun*. 2019;10(1):181.

19. **Ni S**, **Ling Z**, **Wang X**, **et al**. Sensory innervation in porous endplates by Netrin-1 from osteoclasts mediates PGE2-induced spinal hypersensitivity in mice. *Nat Commun*. 2019;10(1):5643.

20. **Tang Y**, **Wu X**, **Lei W**, **et al**. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. *Nat Med*. 2009;15(7):757–765.

21. **Zhen G**, **Cao X**. Targeting TGFβ signaling in subchondral bone and articular cartilage homeostasis. *Trends Pharmacol Sci*. 2014;35(5):227–236.

22. **Chen Y**, **Huang Y-C**, **Yan CH**, **et al**. Abnormal subchondral bone remodeling and its association with articular cartilage degradation in knees of type 2 diabetes patients. *Bone Res*. 2017;5:17034.

23. **Chen Y**, **Hu Y**, **Yu YE**, **et al**. Subchondral trabecular rod loss and plate thickening in the development of osteoarthritis. *J Bone Miner Res*. 2018;33(2):316–327.

24. **Burr DB**, **Radin EL**. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? *Rheum Dis Clin North Am*. 2003;29(4):675–685.

25. **Brazill JM**, **Beeve AT**, **Craft CS**, **Ivanusic JJ**, **Scheller EL**. Nerves in bone: evolving concepts in pain and anabolism. *J Bone Miner Res*. 2019;34(8):1393–1406.

26. **Mapp PI**, **Walsh DA**. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol*. 2012;8(7):390–398.

27. **Zhu S**, **Zhu J**, **Zhen G**, **et al**. Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain. *J Clin Invest*. 2019;129(3):1076–1093.

28. **Zhu J**, **Zhen G**, **An S**, **et al**. Aberrant subchondral osteoblastic metabolism modifies Na$_v$1.8 for osteoarthritis. *Elife*. 2020;9:e57656.

29. **Sayilekshmy M**, **Hansen RB**, **Delaissé J-M**, **Rolighed L**, **Andersen TL**, **Heegaard A-M**. Innervation is higher above bone remodeling surfaces and in cortical pores in human bone: lessons from patients with primary hyperparathyroidism. *Sci Rep*. 2019;9(1):5361.

30. **Gkiatas I**, **Papadopoulos D**, **Pakos EE**, **et al**. The multifactorial role of peripheral nervous system in bone growth. *Front Phys*. 2017;5:6.

31. **Hukkanen M**, **Konttinen YT**, **Rees RG**, **Santavirta S**, **Terenghi G**, **Polak JM**. Distribution of nerve endings and sensory neuropeptides in rat synovium, meniscus and bone. *Int J Tissue React*. 1992;14(1):1–10.

32. **McDougall JJ**. Arthritis and pain. Neurogenic origin of joint pain. *Arthritis Res Ther*. 2006;8(6):220.

33. **Kondo H**, **Togari A**. Continuous treatment with a low-dose β-agonist reduces bone mass by increasing bone resorption without suppressing bone formation. *Calcif Tissue Int*. 2011;88(1):23–32.

34. **Takeda S**, **Elefteriou F**, **Levasseur R**, **et al**. Leptin regulates bone formation via the sympathetic nervous system. *Cell*. 2002;111(3):305–317.

35. **Frost HM**. Tetracycline-based histological analysis of bone remodeling. *Calcif Tissue Res*. 1969;3(3):211–237.

36. **Amling M**, **Takeda S**, **Karsenty G**. A neuro (endo)crine regulation of bone remodeling. *Bioessays*. 2000;22(11):970–975.

37. **Li Z**, **Meyers CA**, **Chang L**, **et al**. Fracture repair requires TrkA signaling by skeletal sensory nerves. *J Clin Invest*. 2019;129(12):5137–5150.

38. **Tomlinson RE**, **Li Z**, **Li Z**, **et al**. NGF-TrkA signaling in sensory nerves is required for skeletal adaptation to mechanical loads in mice. *Proc Natl Acad Sci U S A*. 2017;114(18):E3632–E3641.

39. **Feng BO**, **Wu W**, **Wang H**, **Wang J**, **Huang D**, **Cheng L**. Interaction between muscle and bone, and improving the effects of electrical muscle stimulation on amyotrophy and bone loss in a denervation rat model via sciatic neurectomy. *Biomed Rep*. 2016;4(5):589–594.

40. **Jiang SD**, **Jiang LS**, **Dai LY**. Spinal cord injury causes more damage to bone mass, bone structure, biomechanical properties and bone metabolism than sciatic neurectomy in young rats. *Osteoporos Int*. 2006;17(10):1552–1561.

41. **Sandhu HS**, **Herskovits MS**, **Singh IJ**. Effect of surgical sympathectomy on bone remodeling at rat incisor and molar root sockets. *Anat Rec*. 1987;219(1):32–38.

42. **Sousa-Valente J**, **Calvo L**, **Vacca V**, **Simeoli R**, **Arévalo JC**, **Malcangio M**. Role of TrkA signalling and mast cells in the initiation of osteoarthritis pain in the monoiodoacetate model. *Osteoarthr Cartil*. 2018;26(1):84–94.

43. **Bondeson J**, **Blom AB**, **Wainwright S**, **Hughes C**, **Caterson B**, **van den Berg WB**. The role of synovial macrophages and macrophage-produced mediators in driving inflammatory and destructive responses in osteoarthritis. *Arthritis Rheum*. 2010;62(3):647–657.

44. **Mach DB**, **Rogers SD**, **Sabino MC**, **et al**. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience*. 2002;113(1):155–166.

45. **Oury F**, **Yadav VK**, **Wang Y**, **et al**. CREB mediates brain serotonin regulation of bone mass through its expression in ventromedial hypothalamic neurons. *Genes Dev*. 2010;24(20):2330–2342.

46. **Grässel S**, **Muschter D**. Peripheral nerve fibers and their neurotransmitters in osteoarthritis pathology. *Int J Mol Sci*. 2017;18(5):E931.

47. **Dénes A**, **Boldogkoi Z**, **Uhereczky G**, **et al**. Central autonomic control of the bone marrow: multisynaptic tract tracing by recombinant pseudorabies virus. *Neuroscience*. 2005;134(3):947–963.

48. **Lerner UH**, **Persson E**. Osteotropic effects by the neuropeptides calcitonin gene-related peptide, substance P and vasoactive intestinal peptide. *J Musculoskelet Neuronal Interact*. 2008;8(2):154–165.

49. **Hill EL**, **Elde R**. Distribution of CGRP-, VIP-, D beta H-, SP-, and NPY-immunoreactive nerves in the periosteum of the rat. *Cell Tissue Res*. 1991;264(3):469–480.

50. **Bjurholm A**, **Kreicbergs A**, **Brodin E**, **Schultzberg M**. Substance P- and CGRP-immunoreactive nerves in bone. *Peptides*. 1988;9(1):165–171.

51. **Hukkanen M**, **Konttinen YT**, **Rees RG**, **Gibson SJ**, **Santavirta S**, **Polak JM**. Innervation of bone from healthy and arthritic rats by substance P and calcitonin gene related peptide containing sensory fibers. *J Rheumatol*. 1992;19(8):1252–1259.

52. **Chiu IM**, **von Hehn CA**, **Woolf CJ**. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci*. 2012;15(8):1063–1067.

53. **Imai S**, **Hukuda S**, **Maeda T**. Neonatal capsaicin pretreatment suppresses intramedullary inflammation in adjuvant-induced spondylitis. *Clin Exp Immunol*. 1994;95(1):108–114.

54. **Bär K-J**, **Schaible H-G**, **Bräuer R**, **Halbhuber K-J**, **von Banchet GS**. The proportion of TRPV1 protein-positive lumbar DRG neurones does not increase in the course of acute and chronic antigen-induced arthritis in the knee joint of the rat. *Neurosci Lett*. 2004;361(1–3):172–175.

55. **Edoff K**, **Grenegård M**, **Hildebrand C**. Retrograde tracing and neuropeptide immunohistochemistry of sensory neurones projecting to the cartilaginous distal femoral epiphysis of young rats. *Cell Tissue Res*. 2000;299(2):193–200.

56. **Manzano GM**, **Giuliano LMP**, **Nóbrega JAM**. A brief historical note on the classification of nerve fibers. *Arq Neuropsiquiatr*. 2008;66(1):117–119.

57. **Gerhard D**. Neuroscience. 5th edition. *Yale J Biol Med*. 2013;86(1):113–114.

58. **Zylka MJ**, **Rice FL**, **Anderson DJ**. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgprd. *Neuron*. 2005;45(1):17–25.

59. **Jimenez-Andrade JM**, **Mantyh WG**, **Bloom AP**, **et al**. A phenotypically restricted set of primary afferent nerve fibers innervate the bone versus skin: therapeutic opportunity for treating skeletal pain. *Bone*. 2010;46(2):306–313.

60. **Dellon AL**, **Schneider RJ**, **Burke R**. Effect of acute compartmental pressure change on response to vibratory stimuli in primates. *Plast Reconstr Surg*. 1983;72(2):208–216.

61. **Zelená J**. Survival of Pacinian corpuscles after denervation in adult rats. *Cell Tissue Res*. 1982;224(3):673–683.

62. **Beran R**. Paraesthesia and peripheral neuropathy. *Aust Fam Physician*. 2015;44(3):92–95.

63. **Schaible HG**, **Ebersberger A**, **Von Banchet GS**. Mechanisms of pain in arthritis. *Ann N Y Acad Sci*. 2002;966:343–354.

64. **Hara-Irie F**, **Amizuka N**, **Ozawa H**. Immunohistochemical and ultrastructural localization of CGRP-positive nerve fibers at the epiphyseal trabecules facing the growth plate of rat femurs. *Bone*. 1996;18(1):29–39.

65. **Castañeda-Corral G**, **Jimenez-Andrade JM**, **Bloom AP**, **et al**. The majority of myelinated and unmyelinated sensory nerve fibers that innervate bone express the tropomyosin receptor kinase A. *Neuroscience*. 2011;178:196–207.

66. **Chartier SR**, **Mitchell SAT**, **Majuta LA**, **Mantyh PW**. The changing sensory and sympathetic innervation of the young, adult and aging mouse femur. *Neuroscience*. 2018;387:178–190.

67. **Imai S**, **Tokunaga Y**, **Maeda T**, **Kikkawa M**, **Hukuda S**. Calcitonin gene-related peptide, substance P, and tyrosine hydroxylase-immunoreactive innervation of rat bone marrows: an immunohistochemical and ultrastructural investigation on possible efferent and afferent mechanisms. *J Orthop Res*. 1997;15(1):133–140.

68. **Ivanusic JJ**. Size, neurochemistry, and segmental distribution of sensory neurons innervating the rat tibia. *J Comp Neurol*. 2009;517(3):276–283.

69. **Chuang HH**, **Prescott ED**, **Kong H**, **et al**. Bradykinin and nerve growth factor release the capsaicin receptor from ptdins(4,5)P2-mediated inhibition. *Nature*. 2001;411(6840):957–962.

70. **Cho WG**, **Valtschanoff JG**. Vanilloid receptor TRPV1-positive sensory afferents in the mouse ankle and knee joints. *Brain Res*. 2008;1219:59–65.

71. **Nencini S**, **Ringuet M**, **Kim DH**, **Chen YJ**, **Greenhill C**, **Ivanusic JJ**. Mechanisms of nerve growth factor signaling in bone nociceptors and in an animal model of inflammatory bone pain. *Mol Pain*. 2017;13:1744806917697011.

72. **Shields SD**, **Ahn H-S**, **Yang Y**, **et al**. Nav1.8 expression is not restricted to nociceptors in mouse peripheral nervous system. *Pain*. 2012;153(10):2017–2030.

73. **Duncan CP**, **Shim SS**. J. Edouard Samson Address: the autonomic nerve supply of bone. An experimental study of the intraosseous adrenergic nervi vasorum in the rabbit. *J Bone Joint Surg Br*. 1977;59-B(3):323–330.

74. **GOODALL M**, **KIRSHNER N**. Biosynthesis of epinephrine and norepinephrine by sympathetic nerves and ganglia. *Circulation*. 1958;17(3):366–371.

75. **Anderson CR**, **Bergner A**, **Murphy SM**. How many types of cholinergic sympathetic neuron are there in the rat stellate ganglion? *Neuroscience*. 2006;140(2):567–576.

76. **Brodski C**, **Schnürch H**, **Dechant G**. Neurotrophin-3 promotes the cholinergic differentiation of sympathetic neurons. *Proc Natl Acad Sci U S A*. 2000;97(17):9683–9688.

77. **Bataille C**, **Mauprivez C**, **Haÿ E**, **et al**. Different sympathetic pathways control the metabolism of distinct bone envelopes. *Bone*. 2012;50(5):1162–1172.

78. **Mantyh WG**, **Jimenez-Andrade JM**, **Stake JI**, **et al**. Blockade of nerve sprouting and neuroma formation markedly attenuates the development of late stage cancer pain. *Neuroscience*. 2010;171(2):588–598.

79. **McNamee KE**, **Burleigh A**, **Gompels LL**, **et al**. Treatment of murine osteoarthritis with TrkAd5 reveals a pivotal role for nerve growth factor in non-inflammatory joint pain. *Pain*. 2010;149(2):386–392.

80. **Walsh DA**, **McWilliams DF**, **Turley MJ**, **et al**. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology (Oxford)*. 2010;49(10):1852–1861.

81. **Suri S**, **Walsh DA**. Osteochondral alterations in osteoarthritis. *Bone*. 2012;51(2):204–211.

82. **Pufe T**, **Petersen W**, **Tillmann B**, **Mentlein R**. The splice variants VEGF121 and VEGF189 of the angiogenic peptide vascular endothelial growth factor are expressed in osteoarthritic cartilage. *Arthritis Rheum*. 2001;44(5):1082–1088.

83. **Carmeliet P**, **Tessier-Lavigne M**. Common mechanisms of nerve and blood vessel wiring. *Nature*. 2005;436(7048):193–200.

84. **Vizard TN**, **Newton M**, **Howard L**, **Wyatt S**, **Davies AM**. ERK signaling mediates CaSR-promoted axon growth. *Neurosci Lett*. 2015;603:77–83.

85. **Ohtori S**, **Orita S**, **Yamashita M**, **et al**. Existence of a neuropathic pain component in patients with osteoarthritis of the knee. *Yonsei Med J*. 2012;53(4):801–805.

86. **Rosenberg JM**, **Harrell C**, **Ristic H**, **Werner RA**, **de Rosayro AM**. The effect of gabapentin on neuropathic pain. *Clin J Pain*. 1997;13(3):251–255.

87. **Kurejova M**, **Nattenmüller U**, **Hildebrandt U**, **Selvaraj D**, **Stösser S**, **Kuner R**. An improved behavioural assay demonstrates that ultrasound vocalizations constitute a reliable indicator of chronic cancer pain and neuropathic pain. *Mol Pain*. 2010;6:18.

88. **Donovan-Rodriguez T**, **Dickenson AH**, **Urch CE**. Gabapentin normalizes spinal neuronal responses that correlate with behavior in a rat model of cancer-induced bone pain. *Anesthesiology*. 2005;102(1):132–140.

89. **Dimitri P**, **Rosen C**. The central nervous system and bone metabolism: an evolving story. *Calcif Tissue Int*. 2017;100(5):476–485.

90. **Seidel MF**, **Herguijuela M**, **Forkert R**, **Otten U**. Nerve growth factor in rheumatic diseases. *Semin Arthritis Rheum*. 2010;40(2):109–126.

91. **Obata K**, **Noguchi K**. MAPK activation in nociceptive neurons and pain hypersensitivity. *Life Sci*. 2004;74(21):2643–2653.

92. **Kawamoto K**, **Aoki J**, **Tanaka A**, **et al**. Nerve growth factor activates mast cells through the collaborative interaction with lysophosphatidylserine expressed on the membrane surface of activated platelets. *J Immunol*. 2002;168(12):6412–6419.

93. **Mantyh PW**. The neurobiology of skeletal pain. *Eur J Neurosci*. 2014;39(3):508–519.

94. **Tiseo PJ**, **Kivitz AJ**, **Ervin JE**, **Ren H**, **Mellis SJ**. Fasinumab (REGN475), an antibody against nerve growth factor for the treatment of pain: results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee. *Pain*. 2014;155(7):1245–1252.

95. **García-Castellano JM**, **Díaz-Herrera P**, **Morcuende JA**. Is bone a target-tissue for the nervous system? New advances on the understanding of their interactions. *Iowa Orthop J*. 2000;20:49–58.

96. **Tomlinson RE**, **Li Z**, **Zhang Q**, **et al**. NGF-TrkA signaling by sensory nerves coordinates the vascularization and ossification of developing endochondral bone. *Cell Rep*. 2016;16(10):2723–2735.

97. **Ding Y**, **Arai M**, **Kondo H**, **Togari A**. Effects of capsaicin-induced sensory denervation on bone metabolism in adult rats. *Bone*. 2010;46(6):1591–1596.

98. **Cornish J**, **Callon KE**, **Bava U**, **Kamona SA**, **Cooper GJ**, **Reid IR**. Effects of calcitonin, amylin, and calcitonin gene-related peptide on osteoclast development. *Bone*. 2001;29(2):162–168.

99. **Mrak E**, **Guidobono F**, **Moro G**, **Fraschini G**, **Rubinacci A**, **Villa I**. Calcitonin gene-related peptide (CGRP) inhibits apoptosis in human osteoblasts by β-catenin stabilization. *J Cell Physiol*. 2010;225(3):701–708.

100. **Wang L**, **Shi X**, **Zhao R**, **et al**. Calcitonin-gene-related peptide stimulates stromal cell osteogenic differentiation and inhibits RANKL induced NF-kappaB activation, osteoclastogenesis and bone resorption. *Bone*. 2010;46(5):1369–1379.

101. **Schwab W**, **Bilgiçyildirim A**, **Funk RH**. Microtopography of the autonomic nerves in the rat knee: a fluorescence microscopic study. *Anat Rec*. 1997;247(1):109–118.

102. **Cornish J**, **Reid IR**. Effects of amylin and adrenomedullin on the skeleton. *J Musculoskelet Neuronal Interact*. 2001;2(1):15–24.

103. **Zhou R**, **Yuan Z**, **Liu J**, **Liu J**. Calcitonin gene-related peptide promotes the expression of osteoblastic genes and activates the WNT signal transduction pathway in bone marrow stromal stem cells. *Mol Med Rep*. 2016;13(6):4689–4696.

104. **Zhang Y**, **Xu J**, **Ruan YC**, **et al**. Implant-derived magnesium induces local neuronal production of CGRP to improve bone-fracture healing in rats. *Nat Med*. 2016;22(10):1160–1169.

105. **Schinke T**, **Liese S**, **Priemel M**, **et al**. Decreased bone formation and osteopenia in mice lacking alpha-calcitonin gene-related peptide. *J Bone Miner Res*. 2004;19(12):2049–2056.

106. **Zaidi M**, **Datta HK**, **Chambers TJ**, **MacIntyre I**. Production and characterisation of immunoreactive calcitonin gene-related peptide (CGRP) from a CGRP receptor-positive cloned osteosarcoma cell line (UMR 106.01. *Biochem Biophys Res Commun*. 1989;158(1):214–219.

107. **Guo T-Z**, **Wei T**, **Shi X**, **et al**. Neuropeptide deficient mice have attenuated nociceptive, vascular, and inflammatory changes in a tibia fracture model of complex regional pain syndrome. *Mol Pain*. 2012;8:85.

108. **Azuma H**, **Kido J**, **Ikedo D**, **Kataoka M**, **Nagata T**. Substance P enhances the inhibition of osteoblastic cell differentiation induced by lipopolysaccharide from Porphyromonas gingivalis. *J Periodontol*. 2004;75(7):974–981.

109. **Adamus MA**, **Dabrowski ZJ**. Effect of the neuropeptide substance P on the rat bone marrow-derived osteogenic cells in vitro. *J Cell Biochem*. 2001;81(3):499–506.

110. **Lee H-J**, **Jeong G-S**, **Pi S-H**, **et al**. Heme oxygenase-1 protects human periodontal ligament cells against substance P-induced RANKL expression. *J Periodontal Res*. 2010;45(3):367–374.

111. **Sohn SJ**. Substance P upregulates osteoclastogenesis by activating nuclear factor kappa B in osteoclast precursors. *Acta Otolaryngol*. 2005;125(2):130–133.

112. **Wang L**, **Zhao R**, **Shi X**, **et al**. Substance P stimulates bone marrow stromal cell osteogenic activity, osteoclast differentiation, and resorption activity in vitro. *Bone*. 2009;45(2):309–320.

113. **Wedemeyer C**, **Neuerburg C**, **Pfeiffer A**, **et al**. Polyethylene particle-induced bone resorption in substance P-deficient mice. *Calcif Tissue Int*. 2007;80(4):268–274.

114. **Xiao J**, **Yu W**, **Wang X**, **et al**. Correlation between neuropeptide distribution, cancellous bone microstructure and joint pain in postmenopausal women with osteoarthritis and osteoporosis. *Neuropeptides*. 2016;56:97–104.

115. **Schwartzman RJ**. New treatments for reflex sympathetic dystrophy. *N Engl J Med*. 2000;343(9):654–656.

116. **Calvo W**. The innervation of the bone marrow in laboratory animals. *Am J Anat*. 1968;123(2):315–328.

117. **Tabarowski Z**, **Gibson-Berry K**, **Felten SY**. Noradrenergic and peptidergic innervation of the mouse femur bone marrow. *Acta Histochem*. 1996;98(4):453–457.

118. **Colnot C**, **Lu C**, **Hu D**, **Helms JA**. Distinguishing the contributions of the perichondrium, cartilage, and vascular endothelium to skeletal development. *Dev Biol*. 2004;269(1):55–69.

119. **Dinenno FA**, **Jones PP**, **Seals DR**, **Tanaka H**. Limb blood flow and vascular conductance are reduced with age in healthy humans: relation to elevations in sympathetic nerve activity and declines in oxygen demand. *Circulation*. 1999;100(2):164–170.

120. **Ramasamy SK**, **Kusumbe AP**, **Schiller M**, **et al**. Blood flow controls bone vascular function and osteogenesis. *Nat Commun*. 2016;7:13601.

121. **Jiao K**, **Niu L-N**, **Li Q**, **et al**. β2-Adrenergic signal transduction plays a detrimental role in subchondral bone loss of temporomandibular joint in osteoarthritis. *Sci Rep*. 2015;5:12593.

122. **Togari A**, **Arai M**, **Kondo A**. The role of the sympathetic nervous system in controlling bone metabolism. *Expert Opin Ther Targets*. 2005;9(5):931–940.

123. **Kim B-J**, **Kwak MK**, **Ahn SH**, **et al**. Lower bone mass and higher bone resorption in pheochromocytoma: importance of sympathetic activity on human bone. *J Clin Endocrinol Metab*. 2017;102(8):2711–2718.

124. **Kajimura D**, **Hinoi E**, **Ferron M**, **et al**. Genetic determination of the cellular basis of the sympathetic regulation of bone mass accrual. *J Exp Med*. 2011;208(4):841–851.

125. **Elefteriou F**, **Ahn JD**, **Takeda S**, **et al**. Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature*. 2005;434(7032):514–520.

126. **Brothers SP**, **Wahlestedt C**. Therapeutic potential of neuropeptide Y (NPY) receptor ligands. *EMBO Mol Med*. 2010;2(11):429–439.

127. **Lee NJ**, **Qi Y**, **Enriquez RF**, **et al**. Energy partitioning between fat and bone mass is controlled via a hypothalamic leptin/NPY relay. *Int J Obes (Lond)*. 2020;44(10):2149–2164.

128. **Baldock PA**, **Lee NJ**, **Driessler F**, **et al**. Neuropeptide Y knockout mice reveal a central role of NPY in the coordination of bone mass to body weight. *PLoS One*. 2009;4(12):e8415.

129. **Baldock PA**, **Sainsbury A**, **Couzens M**, **et al**. Hypothalamic Y2 receptors regulate bone formation. *J Clin Invest*. 2002;109(7):915–921.

130. **Igwe JC**, **Jiang X**, **Paic F**, **et al**. Neuropeptide Y is expressed by osteocytes and can inhibit osteoblastic activity. *J Cell Biochem*. 2009;108(3):621–630.

131. **Lee NJ**, **Doyle KL**, **Sainsbury A**, **et al**. Critical role for Y1 receptors in mesenchymal progenitor cell differentiation and osteoblast activity. *J Bone Miner Res*. 2010;25(8):1736–1747.

132. **Persson E**, **Lerner UH**. The neuropeptide VIP potentiates IL-6 production induced by proinflammatory osteotropic cytokines in calvarial osteoblasts and the osteoblastic cell line MC3T3-E1. *Biochem Biophys Res Commun*. 2005;335(3):705–711.

133. **Sun W**, **Tadmori I**, **Yang L**, **Delgado M**, **Ganea D**. Vasoactive intestinal peptide (VIP) inhibits TGF-beta1 production in murine macrophages. *J Neuroimmunol*. 2000;107(1):88–99.

134. **Muschter D**, **Schäfer N**, **Stangl H**, **Straub RH**, **Grässel S**. Sympathetic neurotransmitters modulate osteoclastogenesis and osteoclast activity in the context of collagen-induced arthritis. *PLoS One*. 2015;10(10):e0139726.

135. **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):563–568.

136. **Cherruau M**, **Morvan FO**, **Schirar A**, **Saffar JL**. Chemical sympathectomy-induced changes in TH-, VIP-, and CGRP-immunoreactive fibers in the rat mandible periosteum: influence on bone resorption. *J Cell Physiol*. 2003;194(3):341–348.

137. **Okajima K**, **Harada N**, **Uchiba M**, **Isobe H**. Activation of capsaicin-sensitive sensory neurons by carvedilol, a nonselective beta-blocker, in spontaneous hypertensive rats. *J Pharmacol Exp Ther*. 2004;309(2):684–691.

138. **Kodama D**, **Hirai T**, **Kondo H**, **Hamamura K**, **Togari A**. Bidirectional communication between sensory neurons and osteoblasts in an in vitro coculture system. *FEBS Lett*. 2017;591(3):527–539.

139. **Hu B**, **Lv X**, **Chen H**, **et al**. Sensory nerves regulate mesenchymal stromal cell lineage commitment by tuning sympathetic tones. *J Clin Invest*. 2020;130(7):3483–3498.

140. **Malik KU**, **Sehic E**. Prostaglandins and the release of the adrenergic transmitter. *Ann N Y Acad Sci*. 1990;604:222–236.

141. **Blackwell KA**, **Raisz LG**, **Pilbeam CC**. Prostaglandins in bone: bad cop, good cop? *Trends Endocrinol Metab*. 2010;21(5):294–301.

142. **Huang EJ**, **Reichardt LF**. Trk receptors: roles in neuronal signal transduction. *Annu Rev Biochem*. 2003;72:609–642.

143. **Harrington AW**, **St Hillaire C**, **Zweifel LS**, **et al**. Recruitment of actin modifiers to TrkA endosomes governs retrograde NGF signaling and survival. *Cell*. 2011;146(3):421–434.

144. **Jimenez-Andrade JM**, **Ghilardi JR**, **Castañeda-Corral G**, **Kuskowski MA**, **Mantyh PW**. Preventive or late administration of anti-NGF therapy attenuates tumor-induced nerve sprouting, neuroma formation, and cancer pain. *Pain*. 2011;152(11):2564–2574.

145. **Maruyama K**, **Kawasaki T**, **Hamaguchi M**, **et al**. Bone-protective functions of Netrin 1 protein. *J Biol Chem*. 2016;291(46):23854–23868.

146. **Ke X**, **Li Q**, **Xu L**, **et al**. Netrin-1 overexpression in bone marrow mesenchymal stem cells promotes functional recovery in a rat model of peripheral nerve injury. *J Biomed Res*. 2015;29(5):380–389.

147. **Dun XP**, **Parkinson DB**. Role of Netrin-1 Signaling in Nerve Regeneration. *Int J Mol Sci*. 2017;18(3):E491.

148. **Taniguchi M**, **Yuasa S**, **Fujisawa H**, **et al**. Disruption of semaphorin III/D gene causes severe abnormality in peripheral nerve projection. *Neuron*. 1997;19(3):519–530.

149. **Fukuda T**, **Takeda S**, **Xu R**, **et al**. Sema3A regulates bone-mass accrual through sensory innervations. *Nature*. 2013;497(7450):490–493.

150. **Gomez C**, **Burt-Pichat B**, **Mallein-Gerin F**, **et al**. Expression of Semaphorin-3A and its receptors in endochondral ossification: potential role in skeletal development and innervation. *Dev Dyn*. 2005;234(2):393–403.

151. **Schmelz M**, **Mantyh P**, **Malfait AM**, **et al**. Nerve growth factor antibody for the treatment of osteoarthritis pain and chronic low-back pain: mechanism of action in the context of efficacy and safety. *Pain*. 2019;160(10):2210–2220.

152. **Ekman EF**, **Gimbel JS**, **Bello AE**, **et al**. Efficacy and safety of intravenous tanezumab for the symptomatic treatment of osteoarthritis: 2 randomized controlled trials versus naproxen. *J Rheumatol*. 2014;41(11):2249–2259.

153. **Mayorga AJ**, **Wang S**, **Kelly KM**, **Thipphawong J**. Efficacy and safety of fulranumab as monotherapy in patients with moderate to severe, chronic knee pain of primary osteoarthritis: a randomised, placebo- and active-controlled trial. *Int J Clin Pract*. 2016;70(6):493–505.

154. **Spierings ELH**, **Fidelholtz J**, **Wolfram G**, **Smith MD**, **Brown MT**, **West CR**. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. *Pain*. 2013;154(9):1603–1612.

155. **Guedes V**, **Castro JP**, **Brito I**. Topical capsaicin for pain in osteoarthritis: A literature review. *Reumatol Clin (Engl Ed)*. 2018;14(1):40–45.

156. **Xue P**, **Wang S**, **Lyu X**, **et al**. PGE2/EP4 skeleton interoception activity reduces vertebral endplate porosity and spinal pain with low-dose celecoxib. *Bone Res*. 2021;9(1):36.

157. **Tao Z**, **Zhou Y**, **Zeng B**, **Yang X**, **Su M**. MicroRNA-183 attenuates osteoarthritic pain by inhibiting the TGFα-mediated CCL2/CCR2 signalling axis. *Bone Joint Res*. 2021;10(8):548–557.

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