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Bone Cancer Pain: From Mechanism to Therapy

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Abstract

Purpose of Review—To review how common cancers such as breast, lung, and prostate cancers drive significant and frequently life altering pain when the cells metastasize to bones.

Recent Findings—Similar to cancer, the factors that drive bone cancer pain evolve and change with disease progression. Bone cancer pain has both a nociceptive and neuropathic component. The nociceptive component is driven by the release of algogenic substances by tumor and their associated stromal cells, acidosis caused by bone-destroying osteoclasts, and mechanical destabilization and fracture of the bone. The neuropathic component is induced by tumor cell growth which injures and destroys the distal ends of nerve fibers that normally innervate the bone as well as by inducing a highly pathological sprouting of both sensory and sympathetic nerve fibers.

Summary—There is both a nociceptive and neuropathic component of bone cancer pain. In bone cancer pain there is frequently a continual afferent drive of sensory nerve fibers that induces a peripheral and central sensitization. These mechanistic insights have begun to lead to advances in not only how we understand bone cancer pain but to the development of new therapies to treat bone cancer pain.

Keywords

tumor; stromal cells; metastasis; pain; nerve sprouting

Introduction

Many common cancers including breast, prostate, kidney, and lung, the tumors have a strong predilection to metastasize to bones such as the vertebrae, ribs, hip, femur, and tibia [1] (Fig. 1). Tumor metastasis to bone frequently results in pain, hypercalcemia, anemia, increased susceptibility to infection, skeletal fractures, compression of the spinal cord, spinal instability, and decreased mobility. Bone cancer pain is usually first described as dull in character and constant in presentation, and this pain gradually intensifies with time [2]. As bone remodeling progresses, severe spontaneous pain frequently occurs [3] and the occurrence and severity of this pain can be both acute and unpredictable. This component of bone cancer pain can be particularly debilitating to the patient's functional status and quality

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of life [1, 3-5]. Breakthrough pain, which is an intermittent episode of extreme pain which "breakthroughs" the opiate regiment the patient is on, can occur spontaneously or more commonly is induced by movement of the affected limb or bearing of weight on the tumor-bearing bone(s) [6].

Text of the Review

Current therapies used to treat bone cancer pain

Currently, the treatment of pain from bone metastases involves the use of multiple complementary approaches including radiotherapy, surgery, chemotherapy, bisphosphonates, calcitonin, and analgesics [3, 7]. However, bone cancer pain is one of the most difficult of all chronic pains to fully control [7], as the metastases are generally not limited to a single site, and the efficacy of commonly used analgesics to treat bone cancer pain such as NSAIDS [7] and opioids [7-10] are limited by significant adverse side effects [11, 12].

The unique population of sensory nerves that innervate the bone

Primary afferent sensory neurons are the gateway through which sensory information from peripheral tissues is transmitted to the spinal cord and brain and these sensory nerve fibers innervate every organ of the body with exception of the brain. The cell bodies of sensory fibers that innervate the head and body are housed in the trigeminal and dorsal root ganglia respectively, and can be divided into two major categories, large diameter myelinated A fibers and small diameter unmyelinated C-fibers.

The adult bone receives a restricted and unique innervation as it is only innervated largely by thinly myelinated, TrkA+ sensory nerve fibers (A-delta) and TrkA+ C-fibers (Fig. 2), and receive little, if any, innervation by the larger more rapidly conducting A-beta fibers or the TrkA-negative, unmyelinated peptide poor C-fibers [13, 14]. Recent work has shown that this difference in the population of sensory nerve fibers that innervates the adult skin vs. skeleton begins during perinatal and postnatal development. Several transcription factors including Tlx3 and Runx1 establish the unique phenotype and cohort of sensory nerve fibers that innervate the skin vs. skeleton [15, 16*]. Bones are generally deeper structures located beneath the surface of the skin and likely lack innervation by A-beta sensory nerve fibers because the detection of fine touch, light pressure, and brushing are not required for their function. Therefore, most of the sensory nerves that innervate the bone appear to only be activated by injury or damage to the bone (ie. silent nociceptors). Further studies are required to determine why bone does not receive significant innervation by the TrkA-negative, peptide poor C-fibers (which do richly innervate the skin), although the lack of such innervation clearly suggests there is less nociceptor "redundancy" in bone and joint than in skin (Fig. 2A, B).

Tumor Induced Acidosis, Bone Pain, and Fracture

Once tumor cells such as sarcoma, breast, prostate, thyroid, lung, and renal cancers begin to grow in the bone, a cycle of tumor growth, bone destruction, and formation of woven bone begins, which can result in considerable pain, skeletal fractures, and hypercalcemia [1].

Cancer cells do not destroy bone directly, but rather they and/or their associated stromal cells express the receptor activator of nuclear factor κ-B ligand (RANKL), which binds to its receptor, RANK, that is expressed by osteoclasts. Activation of the RANKL/RANK pathway promotes the proliferation and hypertrophy of these bone-destroying osteoclasts [17, 18]. Osteoclasts resorb bone by forming a highly acidic resorption “bay” or “pit” between the osteoclast and bone that stimulates the TRPV1 or ASIC3 channels expressed by a significant population of nerve fibers that drive bone cancer pain [17, 19] (Fig. 2B).

To attenuate osteoclast induced bone pain, the first and most widely used therapy is the class of compounds known as bisphosphonates that avidly bind to bone. Once bound, osteoclasts that are resorbing bone typically endocytose the breakdown products of bone at the apical (bone facing) surface, transcytose these products, and release them at the distal surface of the osteoclast for disposal by exocytosis [20]. When a bisphosphonate is tightly bound to the bone that is being resorbed, the bisphosphonate will also be taken up by osteocyte endocytosis [21]. Once internalized, the bisphosphonate interferes either with adenosine triphosphate energy metabolism (non-nitrogen–containing bisphosphonates) or with the mevalonate pathway (nitrogen-containing bisphosphonates); both processes result first in osteoclast dysfunction and ultimately in osteoclast apoptosis [21, 22].

Another method that is effective at reducing tumor-induced osteoclast bone resorption in both animals and humans interferes with RANKL binding to RANK, the process required for osteoclast proliferation and maturation [23]. Within two days of administration of therapies that interfere with RANKL binding to RANK (such as osteoprotegrin or denosumab, a sequestering antibody), there is a significant depletion of activated osteoclasts, a marked reduction in plasma markers of bone resorption, and a significant attenuation of bone cancer pain in a mouse model of bone cancer pain [24]. In the past decade, multiple studies revealed that these two classes of therapies reduce osteoclast function and thereby reduce bone cancer pain and tumor-induced bone fracture. The dramatic effects of these therapies can significantly improve the quality of life and functional status of patients with bone cancer [19, 23, 25-27].

Both osteolytic and osteoblastic tumors induce a loss of the mechanical strength and stability of mineralized bone [28], so that with significant bone remodeling, normally innocuous mechanical stress may now result in the distortion and activation of mechanosensitive nerve fibers that innervate the bone. Because bisphosphonates and anti-RANKL therapies reduce tumor induced osteoclast bone remodeling, preserve the mechanical strength of bone, reducing bone fracture, and decrease osteoclast-induced acidosis in both animals and humans, these therapies are highly useful in managing pain caused by cancer metastasis to bone.

Bone cancer pain driven by cancer cells and tumor associated stromal cells

Stromal cells far outnumber cancer cells and include endothelial cells, fibroblasts, as well as a host of inflammatory and immune cells including macrophages, mast cells, neutrophils, and T lymphocytes [29]. Cancer cells and their associated stromal cells secrete a wide variety of factors [29, 30], many of which have previously been shown to sensitize or directly excite primary afferent neurons [31]. These factors include bradykinin,

cannabinoids, endothelins, interleukin-6, granulocyte-macrophage colony-stimulating factor, nerve growth factor (NGF), proteases, and tumor necrosis factor a (Fig. 2C).

One important concept that has emerged over the past decade is that in addition to NGF being able to directly activate TrkA-expressing sensory neurons, this activation appears to play a key role in the sensitization of TRPV1, the retrograde transport of the NGF/TrkA complex to the neuronal cell body of nociceptors induces increases synthesis of the neurotransmitters substance P and calcitonin gene-related peptide, and sodium channels), transcription factors (ATF3), and structural molecules (neurofilaments and the sodium channel-anchoring molecule p11). Additionally, NGF appears to modulate the trafficking and insertion of sodium channels such as Nav 1.8 [32] and TRPV1 [33] in the sensory neurons. NGF also modulates the expression profile of supporting cells in the dorsal root ganglia (DRG) and peripheral nerves, such as nonmyelinating Schwann cells and macrophages [34-36] (Fig. 2C)

In light of the potential role that NGF may play in driving bone cancer pain, therapies that block NGF or TrkA have been investigated for treating breast, prostate, and sarcoma models of bone cancer pain. Even though the prostate cancer cells do not express detectable levels of mRNA coding for NGF [37], in all three models of bone cancer pain, administration of anti-NGF therapy was not only efficacious in reducing both early and late stage bone-related behaviors, but more effective in reducing pain-related behaviors when compared to acute administration of 10 or 30 mg/kg morphine sulfate [37, 38]. Currently, it remains unclear which cell(s) synthesize and release NGF in bone cancer. Previous studies showed that many tumor-associated stromal cells including macrophages, T lymphocytes, mast cells, and endothelial cells are capable of expressing and releasing NGF [39, 40].

Sensory and sympathetic nerve injury and sprouting in the tumor-bearing bone

In the sarcoma, prostate, and breast mouse models of bone cancer, when tumor cells invade the normal tissue, the tumor appears to first come into contact, injure, and then destroy the very distal processes of sensory fibers. This tumor-induced injury and destruction of the distal ends of the sensory nerve fibers that innervate the bone is accompanied by an increase in ongoing and movement-evoked pain behaviors. These studies suggest a component of bone cancer pain is neuropathic in origin [41, 42*].

Another intriguing, but largely unexplored mechanism by which neuropathic skeletal pain may be generated is not by injury, but rather by an active and pathological sprouting and neuroma formation by sensory and sympathetic nerve fibers that innervate the skeleton. To explore this possibility, active nerve sprouting and formation of neuroma-like structures were examined using mouse models of sarcoma, breast, and prostate bone cancer cells growing in the bone marrow [43-45]. In these studies it was noted that there was a remarkable and dramatic sprouting of sensory and sympathetic nerve fibers and these newly sprouted nerve fibers (which can be observed in the periosteum, mineralized bone, and marrow) have a unique morphology, organization, and high density that is never observed in normal bone (Fig. 3A, B). Considering that prostate cancer cells do not express NGF, it is impressive to see how exuberant this sprouting can be as the number of nerve fibers per unit area increased 10-70 times the amount observed in normal bone marrow. This sprouting

appears to require NGF as sustained administration of anti-NGF or Pan-Trk (TrkA, TrkB, TrkC) inhibitor largely blocked the pathological sprouting of sensory nerve fibers, the formation of neuroma-like structures, and significantly inhibited the generation of pain [46, 47*] (Fig. 3C).

Other tyrosine kinase activators induce sensitization in tumor tissues in a manner similar to that of NGF. These activators include artemin [48], granulocyte colony-stimulating factor [49], and granulocyte-macrophage colony-stimulating factor [49], and may play a significant role in promoting tumor-induced sprouting and neuroma formation. Tumor cells are constantly proliferating, metastasizing, undergoing necrosis, and then regrowing at new sites. Thus, even if therapies that block NGF or TrkA are given after tumor-induced sprouting and/or neuroma formation has occurred, these therapies may inhibit new nerve sprouting and neuroma formation. These results emphasize the evolving nature of cancer pain and suggest that the earlier the effective analgesic therapy is administered, the greater the likelihood the therapy will be effective at controlling both peripheral and central sensitization (see section “Bone cancer-induced central sensitization”) that can occur in bone cancer pain. Currently, Tanezumab, a humanized anti-NGF monoclonal antibody is in human clinical trials for bone cancer pain [50-53*]

Bone cancer–induced central sensitization

Several studies have demonstrated that animals with cancer pain also have significant pathological changes in the central nervous system (CNS) that contribute to the generation and maintenance of cancer pain [54]. It has been reported that in mice with bone cancer pain, there are simultaneous changes in the segments of the spinal cord that receive input from nerve fibers that innervate the tumor-bearing tissue. These modifications include concurrent changes in dynorphin, galanin, ATF3, astrocytes (GFAP), microglia, c-Fos expression, and substance-P internalization (Fig. 4)[55].

The possibility that cancer pain also involves changes in the CNS is supported by a recent study of patch-clamp recordings of spinal cord slices with an attached dorsal root. The results of the study demonstrated that tumor-bearing mice exhibit unique plasticity changes in spinal excitatory synaptic transmission mediated through A-δ and C afferent fibers [56]. *In vivo* population studies reveal that in normal animals, the proportions of wide dynamic range (WDR) to nociceptive-specific neurons in this lamina lie at 26% WDR to 74% nociceptive specific. Conversely, with the establishment of cancer pain from a breast cancer model, this ratio shifts to 47% WDR to 53% nociceptive. This phenotypic shift of the superficial dorsal horn population is accompanied by a WDR hyperexcitability to mechanical, thermal, and electrical stimuli in the superficial and deep dorsal horn [57]. This observation strongly correlates with the development of behavioral signs of pain and further suggests that an ongoing state of central sensitization occurs in bone cancer pain.

Conclusions

The mechanisms that drive bone cancer pain evolve with disease progression. Cancer cells and their associated stromal cells can generate ongoing and breakthrough pain that has nociceptive and neuropathic components. The tumor and associated stromal cells release

factors that sensitize and activate bone nociceptors, injure the sensory nerve fibers, and release growth factors that drive ectopic sprouting of nerve fibers and neuroma formation, all of which can contribute to peripheral and central sensitization. These studies have led to the approval of 3 new classes of therapies (bisphosphonates, RANKL inhibitors and alpha 2, delta 1 inhibitors, such as gabapentin, which blocks the neuropathic component of cancer pain as described above.)

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Key Points

- Bone cancer pain has both a nociceptive and neuropathic component.
- Afferent drive from tumor bearing bone induces peripheral and central sensitization.
- Significant nerve sprouting can occur in tumor bearing bone.
- These studies have led to several new therapies being approved to treat bone cancer pain.
- A host of other mechanism based therapies are currently in clinical trials.

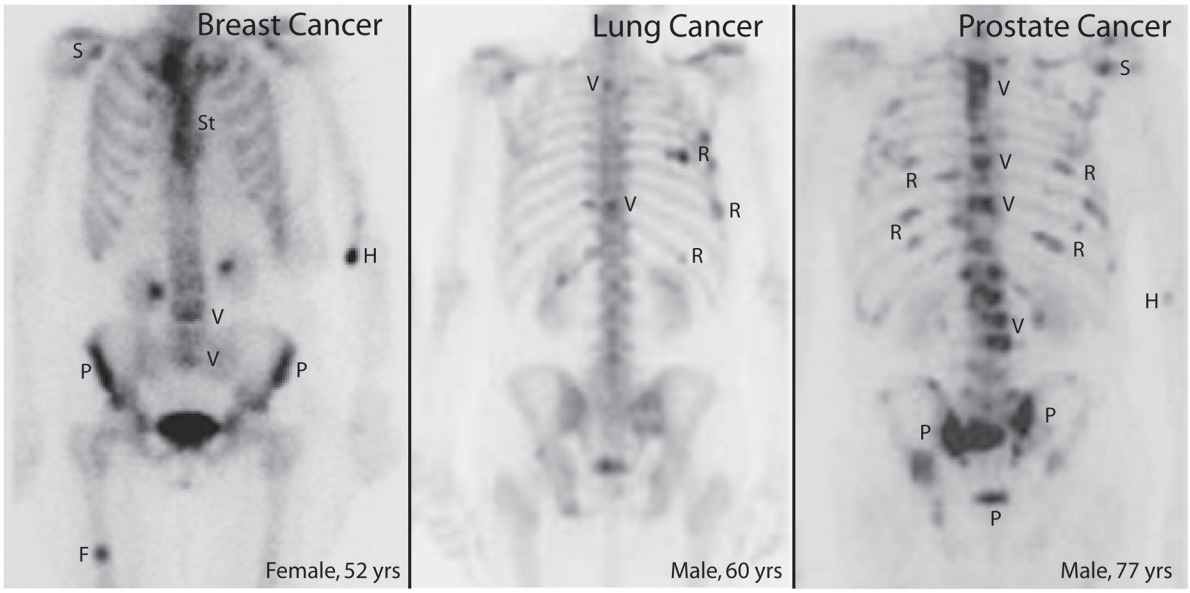

Figure 1. Common cancers metastasize to multiple skeletal sites during disease progression

Technetium-99 bone-scan of male and female patients with active breast, lung, and prostate cancer metastases to multiple skeletal sites. Bone metastasis sites include vertebrae (V), scapula (S), humerus (H), pelvis (P), femur (F), sternum (St), and ribs (R).

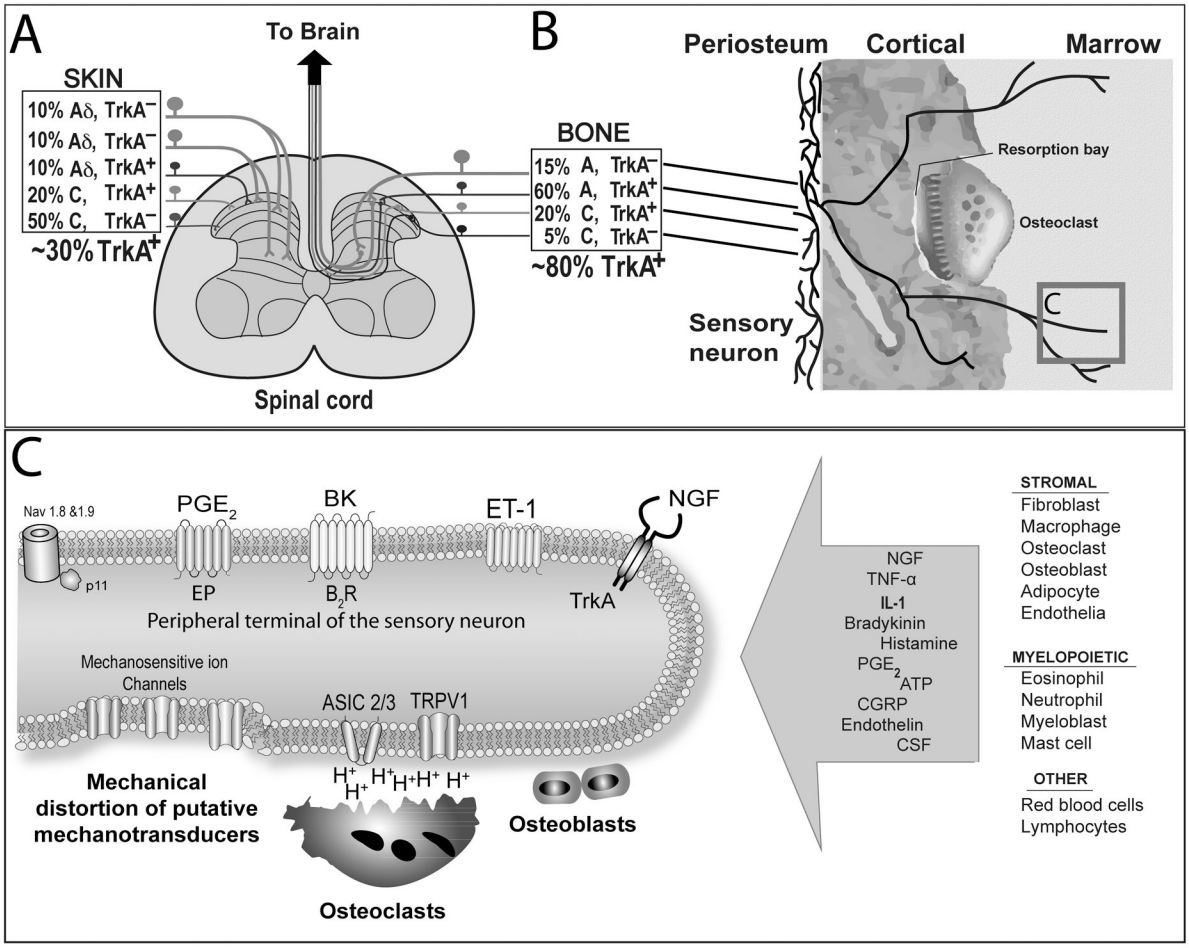

Figure 2. The efficacy of analgesic therapies for cancer-induced skeletal pain may depend on the specific population of sensory neurons that innervate bone and their expression of specific channels, receptors, and transcription factors

(A) Primary afferent neurons innervating the body have their cell bodies in the dorsal root ganglia (DRG) and transmit sensory information from the periphery to the spinal cord and brain. Unmyelinated C fibers and thinly myelinated A-δ fibers contain small diameter cell bodies, which project centrally to the superficial spinal cord. These fibers detect various noxious stimuli: chemical, thermal, and mechanical. Note that although ∼30% of the sensory nerve fibers that innervate the skin are $TrkA^+$, >80% of sensory nerve fibers that innervate bone are $TrkA^+$. The fact that there is a greater percentage of $TrkA^+$ neurons innervating bone compared to skin may in part explain why therapies that block nerve growth factor (NGF) ligand or TrkA receptor show greater efficacy in relieving skeletal pain versus skin pain. **(A, B)** Schematic illustrating the percentage and types of sensory neurons that innervate the skin versus bone. The relative density of A-δ and C sensory fibers is greatest in the periosteum, followed by the bone marrow and mineralized bone; the ratio of the three compartments is 100:2:0.1, respectively. **(C)** Nociceptors use several different types of receptors, ion channels, and transcription factors to detect and transmit signals about noxious stimuli produced by cancer and tumor-associated immune cells. Multiple factors may contribute to the pain associated with cancer. The transient receptor potential

vanilloid receptor 1 (TRPV1) and acid-sensing ion channels (ASICs) detect extracellular protons produced by tumor-induced tissue damage or abnormal osteoclast-mediated bone resorption. Osteoclasts resorb bone through the formation of highly-acidic “bays” between osteoclasts and bone. These “bays” release protons which stimulate acidic-sensitive channels (e.g. TRPV1 and ASICs) expressed on sensory neurons that innervate bone. Several mechanosensitive ion channels may be involved in detecting high-threshold mechanical stimuli that occur when distal processes of sensory nerve fibers are distended from mechanical pressure due to tumor invasion or as a result of destabilization or fracture of bone. Tumor cells and associated inflammatory cells produce a variety of chemical mediators, including prostaglandin (PGE_2), nerve growth factor (NGF), endothelin (ET), bradykinin, and extracellular adenosine triphosphate (ATP). Several of these pro-inflammatory mediators have receptors on peripheral terminals and can directly activate or sensitize nociceptors. NGF, together with its cognate receptor TrkA, may serve as an upstream regulator of bone cancer pain by modulating the sensitivity and increasing the expression of several receptors and ion channels (e.g. Nav 1.8 and TRPV1) that contribute to the increased excitability of nociceptors in the vicinity of the tumor.

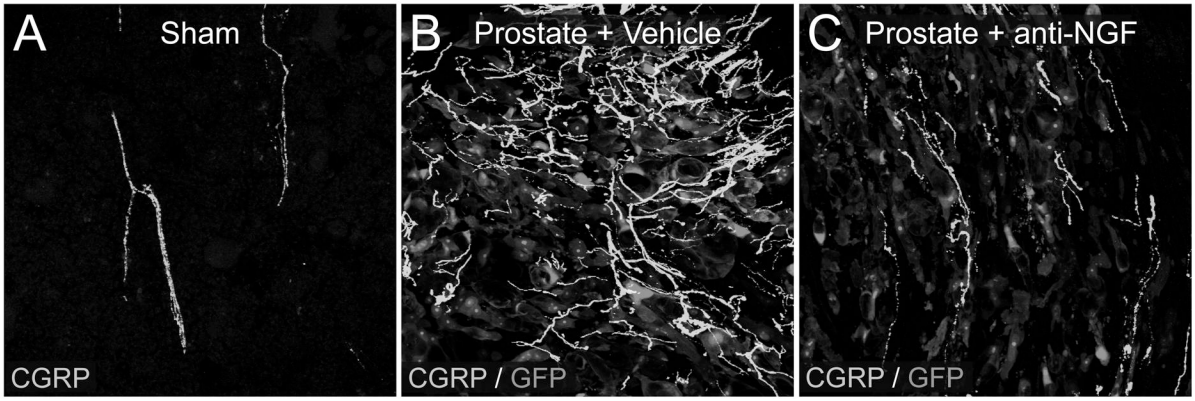

Figure 3. Preventative sequestration of nerve growth factor (NGF) reduces cancer-induced sprouting of CGRP$^+$ sensory nerve fibers in the bone

(A) In sham-operated mice, CGRP$^+$ nerve fibers display a linear, homogenous morphology typical of CGRP$^+$ innervation in the bone marrow. **(B)** As prostate cancer cells (transfected by green fluorescent protein (GFP)) grow within the bone marrow and form small colonies of cancer cells there is a dramatic sprouting of CGRP$^+$ nerve fibers within or surrounding the tumor colonies. **(C)** Preventative sequestration of NGF (mAb911, 10 mg/kg, i.p., given at days 10, 15, 20, and 25 post cell-injection) significantly reduces the pathological, tumor-induced sprouting and reorganization of CGRP$^+$ sensory neurons. Images were acquired at the metaphyseal region of the bone marrow and were projected from 40 optical sections at 0.5 μm intervals.

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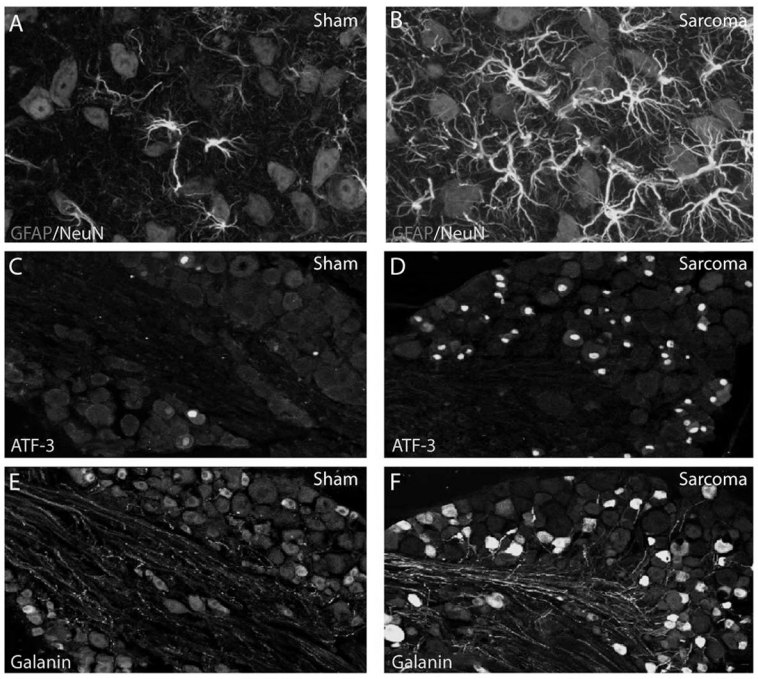

Figure 4. Bone-cancer induces the upregulation of neuropeptides and transcription factors associated with neuronal damage, resulting in central sensitization

Confocal images showing that the expression of astrocyte marker glial fibrillary acidic protein (GFAP) (A,B), activated transcription factor-3 (ATF-3) (C,D), and galanin (E,F) is upregulated in primary sensory neurons that innervate the tumor bearing bone following injection of sarcoma tumor cells into the mouse femur. **(A, B)** Coronal sections of the L4 spinal cord 21 days following injection of osteolytic sarcoma cells into the intramedullary space of the femur. High magnification of GFAP in the contralateral (A) and ipsilateral (B) sides of the tumor-bearing bone shows that in the ipsilateral side there is marked hypertrophy of astrocytes characterized by an increase in both the size of the astrocyte cell bodies and the extent of the arborization of their distal processes. Additionally, this increase in GFAP is observed without a detectable loss of neurons, as NeuN labeling remains unchanged. These images, from 60 μm thick tissue, are projected from 12 optical sections acquired at 0.8 μm intervals with a 60× lens. **(C, D, E, F)** ATF-3 and galanin are upregulated in primary sensory neurons that innervate the tumor-bearing femur 14 days following injection of osteolytic sarcoma cells into intramedullary space of the femur. Neurons in the sham-vehicle L2 dorsal root ganglia (DRG) express low levels of both ATF-3 (C) or the neuropeptide galanin (E), whereas 14 days following injection and confinement of sarcoma cells to the marrow space there is a marker upregulation of both ATF-3 (D) and galanin (F) in sensory neurons in the L2 DRG ipsilateral to the tumor-bearing bone. These data suggest that tumor cells invading bone injure the sensory nerve fibers that normally innervate the tumor-bearing bone.

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