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New Insights in Understanding and Treating Bone Fracture Pain

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Abstract

Purpose of Review—This paper describes recent advances in understanding the mechanisms that drive fracture pain and how these findings are helping develop new therapies to treat fracture pain.

Recent Findings—Immediately following fracture, mechanosensitive nerve fibers that innervate bone are mechanically distorted. This results in these nerve fibers rapidly discharging and signaling the initial sharp fracture pain to the brain. Within minutes to hours, a host of neurotransmitters, cytokines, and nerve growth factor are released by cells at the fracture site. These factors stimulate, sensitize, and induce ectopic nerve sprouting of the sensory and sympathetic nerve fibers which drive the sharp pain upon movement and the dull aching pain at rest. If rapid and effective healing of the fracture occurs, these factors return to baseline and the pain subsides, but if not, these factors can drive chronic bone pain.

Summary—New mechanism-based therapies have the potential to fundamentally change the way acute and chronic fracture pain is managed.

Keywords

Skeletal; Nociceptors; Nerve growth factor; Pediatric; Genetic disorders; Geriatric

Introduction

Fractures and fracture pain are two of the most common and costly problems caused by bone injury or diseases [1, 2]. Fractures that are severe and/or do not heal appropriately can be highly debilitating and have a remarkably negative impact on an individual's quality of life

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Compliance with Ethical Standards

Conflict of Interest Stefanie Mitchell and Lisa Majuta declare no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of major importance

and functional status [3–5]. Unlike the skin, where nonuse promotes healing, effective healing of a fractured load-bearing bone (i.e., femur, hip, vertebrae) demands the patient to move, use, and mechanically load the injured bone. To optimize bone healing, while minimizing loss of bone and muscle mass, minimal bed rest is recommended following fracture. Thus, in both young and old patients alike, the rehabilitation regimens require the patient to move and place weight on the fractured bone in the first day after fracture stabilization. The most common reason that many patients cannot fully participate in this rehabilitation is that we currently do not have effective side effect-free analgesics that can attenuate bone fracture pain [6••, 7, 8]. If this pain cannot be effectively attenuated, the necessary bone loading and bone healing can be delayed, or does not occur at all, resulting in loss of muscle and bone mass, loss of mobility, and a significant increase in morbidity and mortality [9].

Currently, the treatment of pain following skeletal fracture of a load-bearing bone involves stabilization of the fractured bone, minimal bed rest, and usually the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates to control the pain [6••, 10]. While NSAIDs can be effective in attenuating musculoskeletal pain, reports suggest that they can inhibit fracture healing in mice, rats, and humans [8, 11, 12]. Thus, NSAIDs and cyclooxygenase-2 (COX-2) inhibitors can retard callus formation and bone formation at the fracture site. In turn, this can result in delayed bone healing, increased incidence of fracture non-union, and decreased bone strength [13••, 14, 15]. While this issue as to the extent to which NSAIDs inhibit human bone healing remains unclear, many orthopedic surgeons believe that the use of NSAIDs is contraindicated in patients with bone fracture [16–18].

Although opiates are commonly used to control significant bone fracture pain, compared to placebo, opioids are not very effective in controlling chronic skeletal pain and long-term opiate use in patients with chronic skeletal pain interferes with functional status and the ability of the patient to return to work [19, 20, 21••, 22]. In young individuals with painful bone fractures, long-term opiate use can result in dependence, reduced functional status, and are less likely to return to work [21••]. In light of the above listed problems with both NSAIDS and opiates, development of novel, mechanism-based therapies to attenuate fracture pain is a clear priority for young, adult, and aging patients with acute and chronic bone fracture pain [6••].

Models of Bone Fracture Pain

Given the enormous consequences that fracture pain can have in terms of human suffering and medical costs, it is surprising that until recently, there was not an established animal model for studying bone fracture pain. To develop such a model, the rodent closed femur fracture model [23–25] was used as a starting point, as this model had been successfully employed by the bone research community to explore the effects of various anabolic and anti-resorptive therapies on bone remodeling and bone healing (Fig. 1). To develop a fracture pain model, indices of fracture pain such as nocifensive behaviors and activity monitoring were added. Once these models of bone fracture pain were established [26, 27••, 28] and validated [29], in many ways, these models are similar to the sequence of events observed in humans following bone fracture. Thus, in rodents, pain behaviors were apparent

immediately following fracture which included increased guarding and flinching, reduced load bearing on the fractured bone, and an overall decrease in horizontal activity (Fig. 2). If rapid and effective healing occurred, these behaviors were generally extinguished by 14–28 days post-fracture in young adult male and female rodents [26, 27••, 28–30, 31••, 32••]. However, if effective fracture healing did not occur, many of these fracture pain-related behaviors were still present at 6–9 months post-fracture [33•].

Mechanisms that Drive Bone Fracture

Fracture Activates Mechanosensitive Channels that Are Expressed by Sensory Neurons which Innervate Bone

Immediately following bone fracture, mechanosensitive nerve fibers that innervate bone are mechanically distorted resul ting in these nerve fibers rapidly discharging and signaling the initial injury to the spinal cord and brain [34–36]. Many of these mechanosensitive nerve fibers that detect and signal the initial fracture pain are located in the periosteum which is tightly opposed to the outer cortical wall of mineralized bone [36]. Previous studies have shown that many of the sensory nerve fibers that innervate the periosteum are mechanosensitive C and A-delta nociceptors [34, 37, 38, 39•] that rapidly respond to mechanical distortion of the adjacent bone or increased intraosseous pressure [37, 40, 41]. Following bone fracture, any movement or loading of the fractured bone would be expected to result in mechanical stimulation of mechanosensitive sensory nerve fibers that innervate the periosteum, mineralized bone, and marrow [27••, 28, 37, 42, 43]. Thus, normally, non-noxious loading of the bone will distort the mechanosensitive nerve fibers so that even normally innocuous movement or loading of the fractured bone will now be perceived as a highly noxious event.

Activation and Sensitization of Bone Nociceptors

Within minutes of bone fracture, a wide variety of stromal and inflammatory cells release mediators that can directly activate or sensitize nociceptors that normally innervate the bone. These mediators include prostaglandins [6••, 44], bradykinin [45], endothelins [46], and nerve growth factor [27••, 31••] which have all been shown to excite and/or sensitize nociceptors that innervate the bone. Interestingly, therapies targeting these mediators have been shown to relieve a variety of human skeletal pains in animals and humans including osteoarthritis, low back pain, and bone cancer pain [47, 48••]. One molecule that appears to be particularly effective in sensitizing bone nociceptors is nerve growth factor (NGF) [32••, 37]. When NGF binds to its cognate receptor tropomyosin receptor kinase A (TrkA), a variety of mechanotransducers, ion channels, receptors, and neurotransmitters expressed by nociceptors appear to be sensitized and/or upregulated [32••, 49] so that normally innocuous stimulation of a bone nociceptor is now per-ceived as a noxious event (Fig. 3).

Nerve Injury and Ectopic Nerve Sprouting Following Bone Fracture

Following bone fracture, mechanical injury to sensory or sympathetic nerve fibers that innervate the bone may occur generating a neuropathic pain state [27••, 28]. One other mechanism that may be involved in driving bone fracture pain is ectopic nerve sprouting (Fig. 4). Following bone fracture, several neurotrophic factors, including NGF, are released

by stromal and inflammatory cells, which can induce an exuberant and highly ectopic sprouting resulting in hyper-innervation of the marrow, mineralized bone, and periosteum [33•]. Importantly, NGF can not only induce ectopic nerve sprouting into areas of bone that are normally poorly innervated, but can also sensitize these newly sprouted nerve fibers so normal loading or movement of the fractured bone is perceived as a highly noxious event [6••, 37]. While ectopic sprouting of sensory/sympathetic nerve fibers probably occurs in the callus at most fracture sites [50], with rapid and effective bone healing, NGF levels decline and these newly sprouted nerve fibers are "pruned" back resulting in a normal innervation of the bone and non-sensitized nociceptors [51]. However, if normal and effective fracture healing does not occur, this ectopic nerve sprouting in the non-resorbed callus can persist [33•, 51] so that mechanical strain and/or distortion of still weak and non-healed bone may result in normally innocuous movement and loading of the fracture site now being perceived as a noxious event.

Central Sensitization

While the present review has focused on advances made in understanding the peripheral mechanisms that drive bone fracture pain, what is also clear is that following bone fracture, the brain will also undergo sensitization (i.e., "central sensitization") that amplifies the perception and severity of pain [52••, 53]. Central sensitization is thought to occur when the chemical, electrophysiological, and pharmacological systems that transmit and modulate pain are altered in the spinal cord and brain so that normal use and movement of the bone is now perceived as a noxious event [54].

It should be emphasized that we do not yet know the specific mechanisms that generate central sensitization. However, what we do know is that injury to the skeletal system seems to be much more effective at inducing central sensitization as compared to injury to skin. For example, in 1986, Woolf and Wall noted "…a twisted ankle invokes relatively little destruction of tissue and elicits an abrupt localized stabbing pain that dies down quickly but is followed by a prolonged period of spreading, poorly localized deep pain, and tenderness that affects reflexes and gait. In contrast, localized skin damage produces an acute burst of pain that gradually dies down over minutes but is associated with a spatially restricted response of flair, wheal and surrounding tenderness" [55]. These authors also noted that small skin lesions produce comparatively less widespread and prolonged disturbances to sensation and reflex patterns than injuries to the skeleton [55].

Mechanism-Based Therapies to Control Bone Fracture Pain

Although bone fractures are a common cause of chronic pain and long-term physical disability (especially in the elderly where bone healing is slower and frequently incomplete), there are currently relatively few pharmacological therapies that can fully manage the pain and stimulate fracture repair without significant, unwanted side effects. However, in the last decade, significant progress has been made. Thus, in terms of bone fracture pain, we now know that the bone is innervated by a limited repertoire of sensory nerve fibers [37, 49, 56] (Fig. 5) and that many forms of skeletal pain have both a nociceptive and a neuropathic component [6••]. We also know that the majority of sensory nerve fibers that innervate the

bone express TrkA and thus respond to NGF that is released at the site of bone fracture. Furthermore, we know that sensory and sympathetic nerve fibers in an injured or diseased skeleton also display a remarkable neurochemical and morphological plasticity by upregulating neurotransmitters, cytokines, growth factors, and receptors and undergoing an exuberant nerve sprouting that is never observed in the normal skeleton [33•, 57]. Additionally, sequestration of NGF or inhibition of TrkA can result in significant attenuation of skeletal pain [27••, 29, 32••, 47, 48••, 57–62].

Progress has also been made in beginning to identify molecules that may speed up fracture healing. Thus, sclerostin has now been identified as a protein that is expressed and released by osteocytes [3, 63] and when it is present in high levels, it inhibits bone formation and slows down fracture healing [64••, 65]. With aging, the incidence of low-trauma fractures increases and the rate of rapid and effective bone fracture healing decreases. Inhibition of sclerostin (with antibodies that sequester sclerostin) may reduce the likelihood of fragility fractures, stimulate more rapid and effective fracture healing, and thereby reduce the incidence and duration of skeletal pain that frequently accompanies failed healing of bone fractures. Thus, preclinical and human studies suggest that inhibition of endogenous sclerostin builds bone and promotes fracture healing in the young and aging bone [3••, 64••].

Conclusions

We are only beginning to understand the mechanisms that drive fracture pain. Whether mechanism-based therapies such as anti-NGF, TrkA inhibitors, or anti-sclerostin receive approval for broad use in humans will depend on their safety profile. However, NGF and its cognate receptor TrkA clearly play major roles in driving bone fracture pain and sclerostin plays a major role in driving the age-related decline in fracture healing. A better understanding of the mechanisms that drive bone fracture pain as well as the factors that control bone healing in the young, adult, and aging bone has the potential to transform our ability to better manage fracture pain whether the bone fracture is due to injury, disease, or aging.

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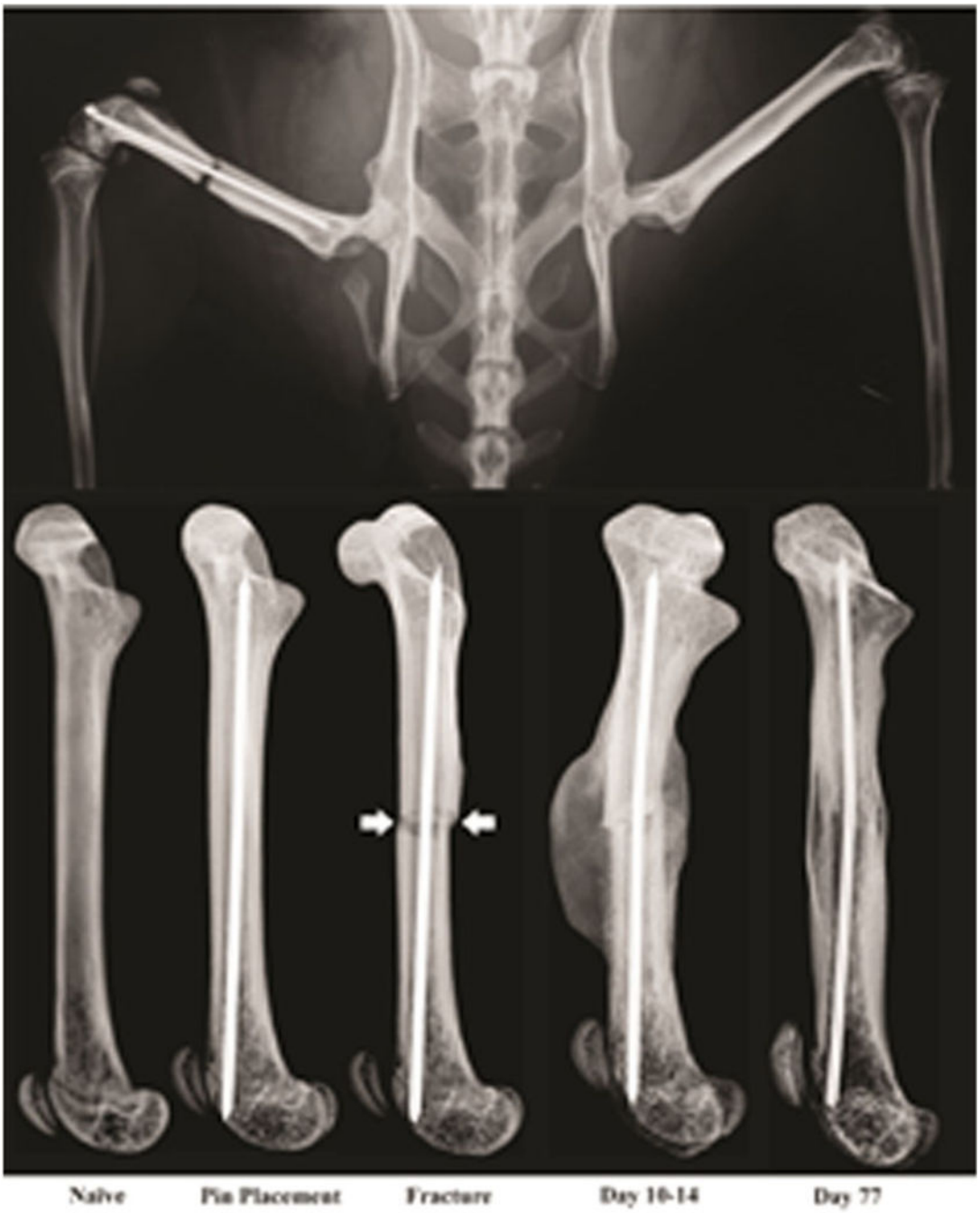

Fig. 1.

Representative radiographs showing the rodent model of bone fracture pain. Note that in the top image, a titanium pin has been placed in the intramedullary space of the right femur before the fracture (to stabilize the fractured bone) and a fracture has been made in the middle of the femur. Pain is immediately evident following bone fracture and with normal bone healing (callous formation, mineralization, resorption, and cortical union), the fracture pain subsides. These images are from a mouse but a nearly identical model has also been developed in rats

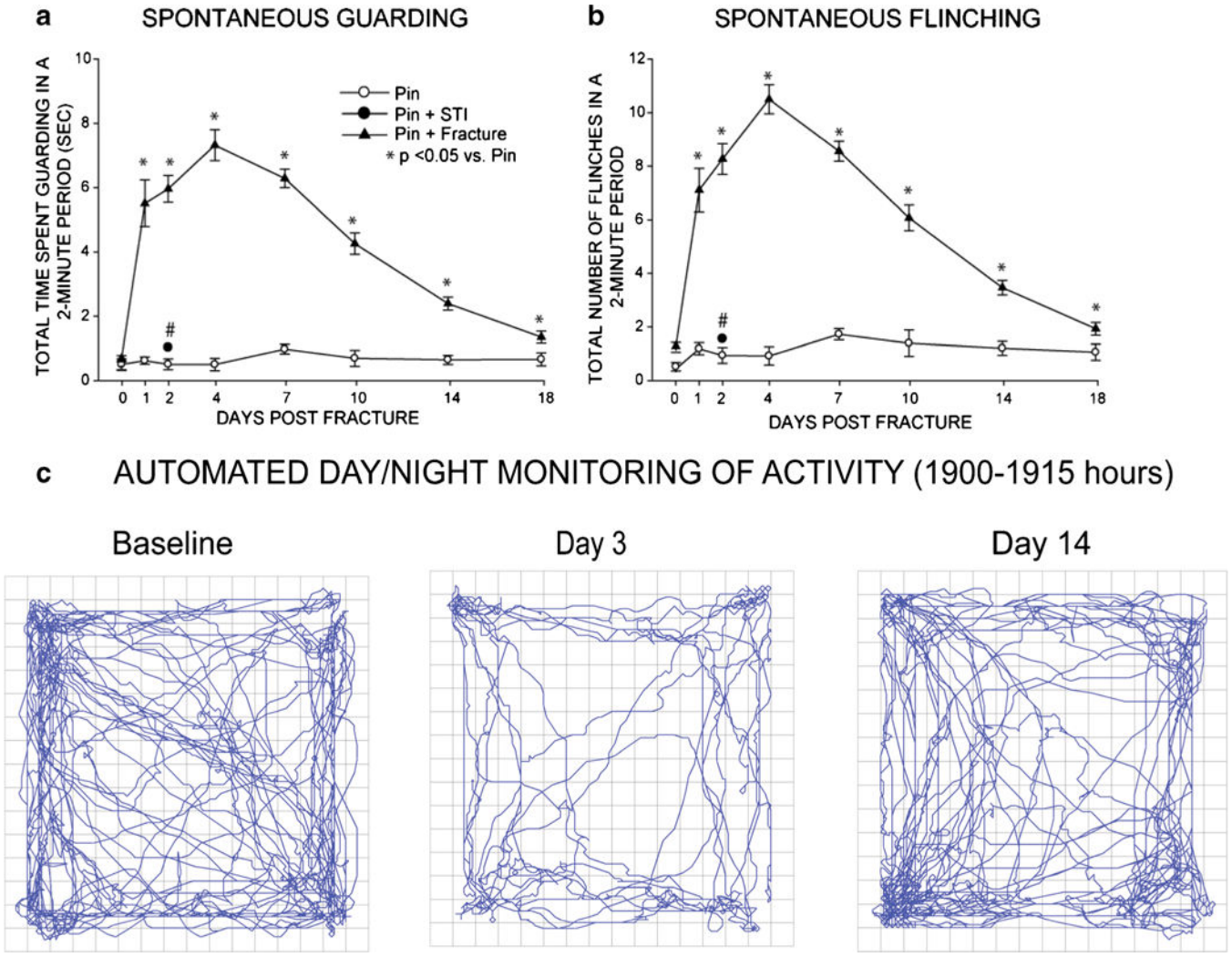

Fig. 2.

Quantification of pain-related behaviors following bone fracture. Bone fracture pain can be assessed by measuring spontaneous guarding (**a**) and spontaneous flinching (**b**) of the right hindlimb over a 2-min observation period during the day. Pain behaviors can also be assessed by using 20 h day/night activity monitoring of horizontal (**c**), vertical and velocity of movement of the mice following fracture. The pictographs in (**c**) show the spontaneous horizontal activity at baseline (1 day prefracture), day 3 post-fracture, and day 14 post-fracture. In general, in young mice, if effective bone healing occurs, fracture-induced pain-related behaviors peak at 1–4 days post-fracture and return to baseline by day 21 days post-fracture. Note that in mice, placement of the stainless-steel pin or impactor-induced soft tissue injury (STI) alone with no bone fracture shows little change in either spontaneous guarding (**a**) or flinching (**b**)

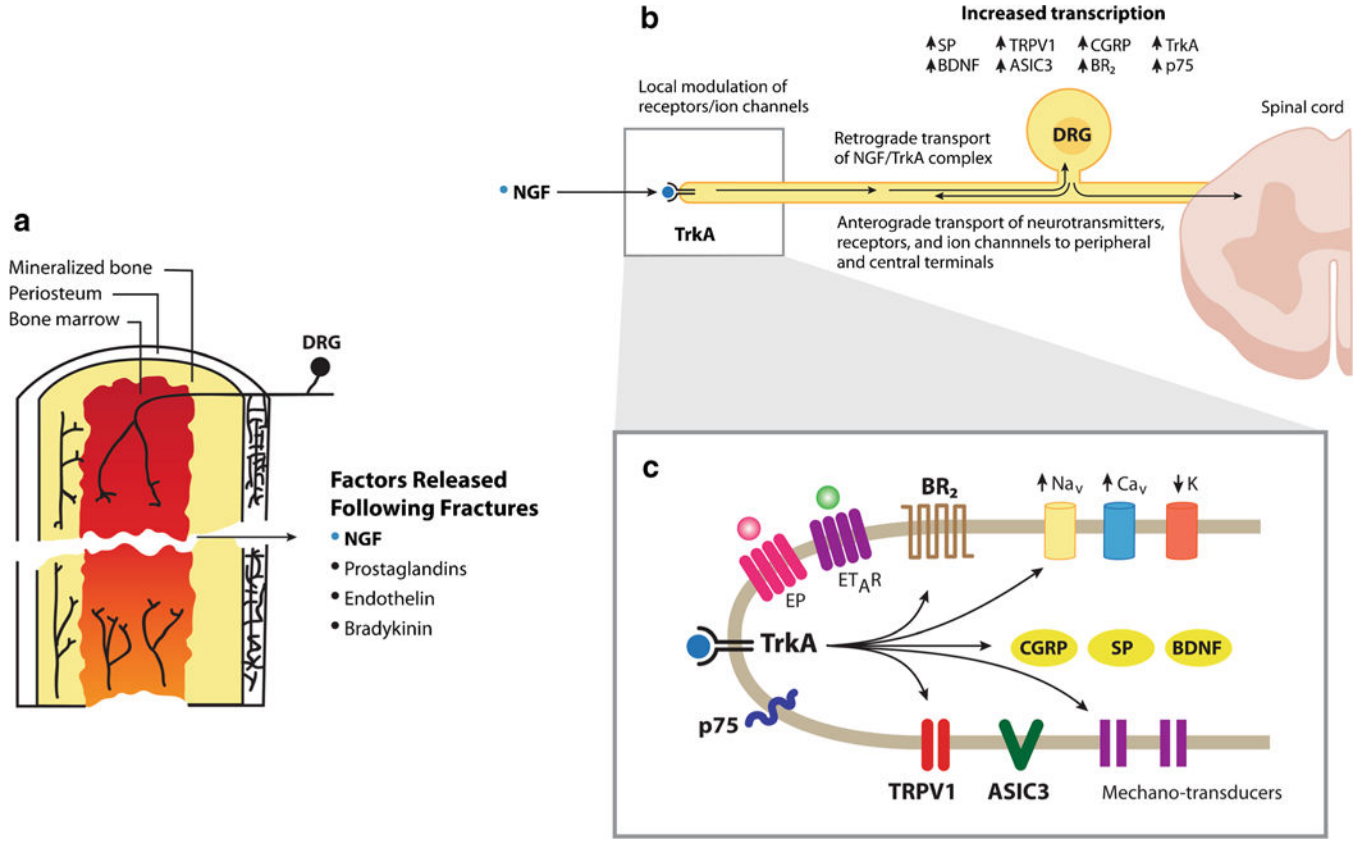

Fig. 3.

Schematic illustrating the sensory nerve fibers that innervate the femur and some of the factors that may contribute to fracture-induced skeletal pain. Sensory nerve fibers that innervate the bone (**a**) are generally mechanosensitive and are present in the periosteum (the thin cellular and fibrous sheath that surrounds the outer surface of the mineralized bone), cortical bone, and bone marrow. Following bone fracture, a variety of factors are released at the fracture site including nerve growth factor (NGF), prostaglandins, endothelins, and bradykinin which activate and/or sensitize neurons that convey information from the bone to the spinal cord (**b**) in that NGF binds to its cognate receptor tropomyosin receptor kinase A (TrkA) and the NGF/TrkA complex is then retrogradely transported to the cell body of the sensory neuron where it induces upregulation of a variety of neurotransmitters, receptors, and ion channels involved in detecting and transmitting noxious stimuli from the bone to the spinal cord and brain. In sensory nerve fibers at the fracture site (**c**), NGF also directly sensitizes a variety of receptors, ion channels, and mechanotransducers expressed by sensory nerve fibers that innervate the bone so that normally innocuous stimulation of the bone is now perceived as noxious stimuli

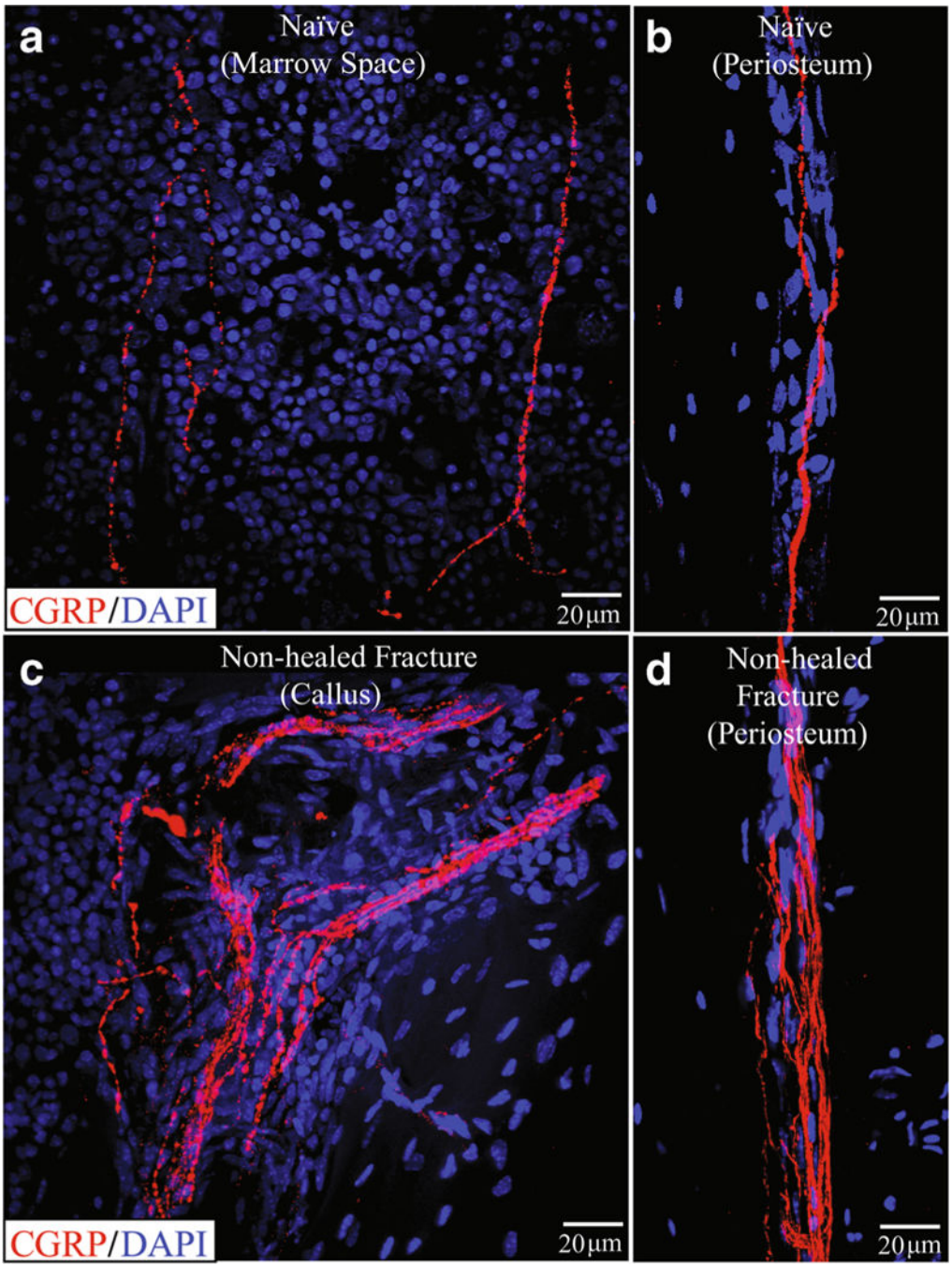

Fig. 4.

Sprouting of sensory nerve fibers at an unhealed fracture site 6 months following bone fracture where desired healing of the fracture has not occurred. In these confocal images, sensory nerve fibers are labeled with an antibody raised against calcitonin gene-related peptide (CGRP, red). Note that in the normal uninjured femur (**a, b**), there are a few new fibers in the bone marrow (**a**) and in the periosteum (**b**). However, in the non-healed fracture, there is a marked increase in the density of sensory nerve fibers in both the callous (**c**) and in the periosteum (**D**). This “hyper-innervation” of the bone at the unhealed fracture site is

never observed in the normal femur and may contribute to the chronic limping and pain-related behaviors observed in animals with non-healed fractures

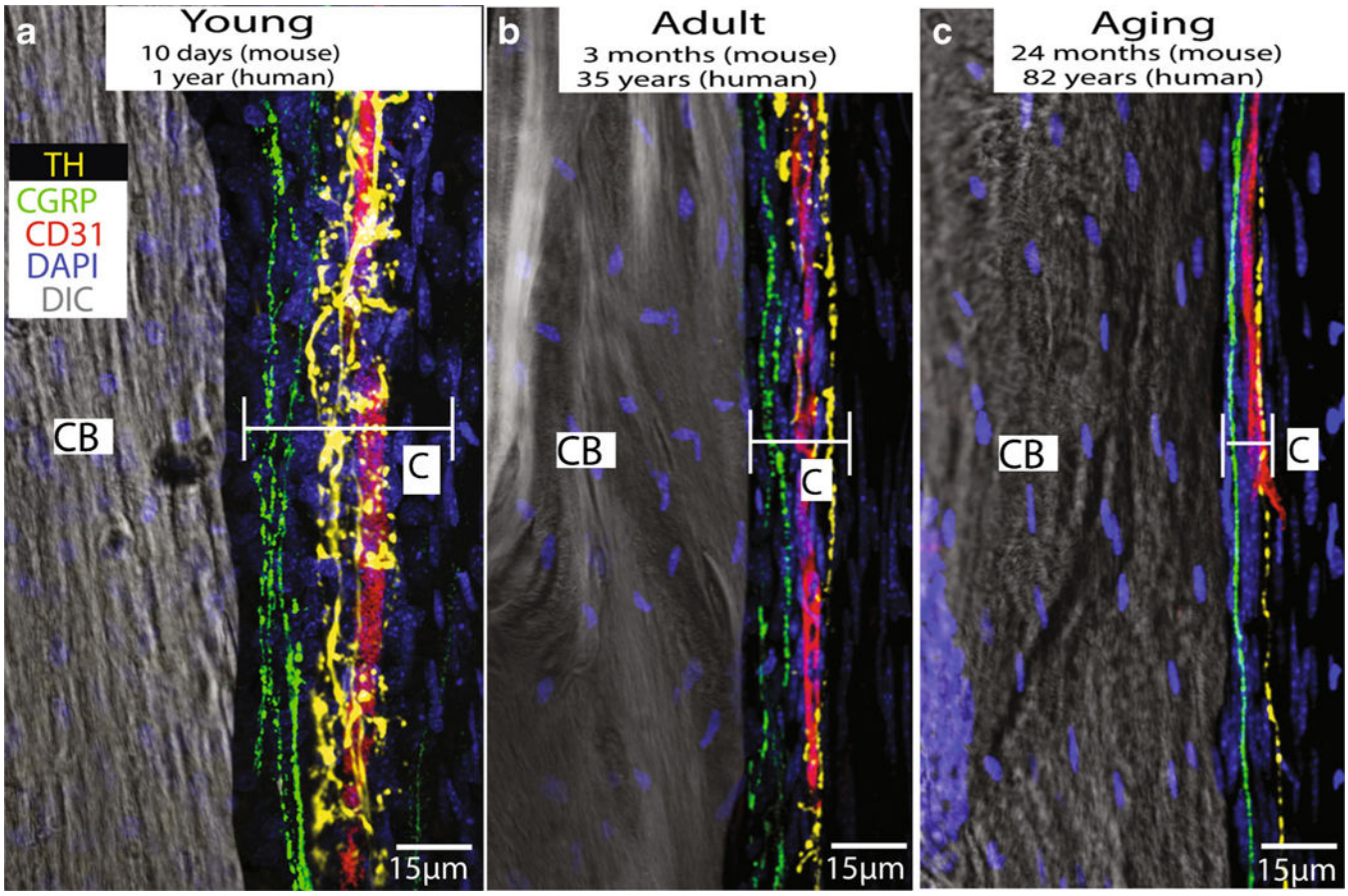

Fig. 5.

Images showing that sympathetic nerve fibers (yellow), sensory nerve fibers (green), and blood vessels (red) are present and have a similar organization in the periosteum of the young, adult, and aging mouse femur. The periosteum is a thin cellular and fibrous sheath that is tightly opposed to the outer surface of all bones of the body and probably plays a major role in detecting bone fracture and the generation of acute and chronic fracture pain. These data would suggest that even in the very young and very old, the periosteum is richly innervated by sensory and sympathetic nerve fibers and these nerve fibers probably play a significant role in the detection and signaling of fracture pain throughout the lifespan. In these images, blood vessels are labeled with an antibody raised against CD-31, primary afferent sensory nerve fibers are labeled with an antibody raised against calcitonin gene-related peptide (CGRP), and sympathetic nerve fibers are labeled with an antibody raised against tyrosine hydroxylase (TH)