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Review

Fracture pain—Traveling unknown pathways

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ABSTRACT

An increase of fracture incidence is expected for the next decades, mostly due to the undeniable increase of osteoporotic fractures, associated with the rapid population ageing. The rise in sports-related fractures affecting the young and active population also contributes to this increased fracture incidence, and further amplifies the economical burden of fractures. Fracture often results in severe pain, which is a primary symptom to be treated, not only to guarantee individual's wellbeing, but also because an efficient management of fracture pain is mandatory to ensure proper bone healing. Here, we review the available data on bone innervation and its response to fracture, and discuss putative mechanisms of fracture pain signaling. In addition, the common therapeutic approaches to treat fracture pain are discussed.

Although there is still much to learn, research in fracture pain has allowed an initial insight into the mechanisms involved. During the inflammatory response to fracture, several mediators are released and will putatively activate and sensitize primary sensory neurons, in parallel, intense nerve sprouting that occurs in the fracture callus area is also suggested to be involved in pain signaling. The establishment of hyperalgesia and allodynia after fracture indicates the development of peripheral and central sensitization, still, the underlying mechanisms are largely unknown. A major concern during the treatment of fracture pain needs to be the preservation of proper bone healing. However, the most common therapeutic agents, NSAIDS and opiates, can cause significant side effects that include fracture repair impairment. The understanding of the mechanisms of fracture pain signaling will allow the development of mechanisms-based therapies to effectively and safely manage fracture pain.

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Abbreviations: ASIC3, Acid-sensing ion channel 3; BDNF, Brain-derived neurotrophic factor; BMP, Bone morphogenetic proteins; CGRP, Calcitonin gene-related peptide; COX, Cyclooxygenase; CRPS, Complex Regional Pain Syndrome; DRG, Dorsal root ganglia; GAP43, Growth-associated protein 43; GDF8, Growth and differentiation factor 8; GDNF, Glial cell line-derived neurotrophic factor; IB4, Isolectin B4; IL, Interleukin; Mrgprd, Mas related G protein-coupled receptors; NGF, Nerve growth factor; NPY, Neuropeptide Y; NSAIDs, Non-steroidal anti-inflammatory drugs; PACAP, Pituitary adenylate cyclase activating peptide; Sema3A, Semaphorin 3 A; SP, Substance P; TGF-beta, Transforming growth factor-beta; TNF-alpha, Tumor necrosis factor-alpha; TrkA, Tropomyosin receptor kinase A; TRPV1, Transient receptor potential vanilloid 1; VIP, Vasoactive intestinal peptide.

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1. Introduction

The rapid population ageing and the associated intrinsic high incidence of osteopenia and osteoporosis are expected to cause an increase in the number of fractures in the coming decades [1]. It is estimated that 40 to 50% of women and 13 to 22% of men will suffer an osteoporotic fracture at some point in their life [2–4]. Also, the spectrum of fractures in the older population is changing [1,5]. Alterations in lifestyle, with older people being more active, are suggested to contribute to an increase in incidence and a change in the type of fracture in the elderly [6]. It has been recognized that osteoporotic fractures are becoming a major health problem, accounting for a significant fraction of healthcare costs [7,8].

Regarding the young population, the incidence of sports-related fractures is a serious concern [6,9]. In fact, sports activities are the third most common cause of fractures in the population as an all, after falls in the elderly and direct blows or assaults [6,9]. The growing practice of sports activities [10,11] is likely to increase the incidence of sports-related fractures in young and active population, thus amplifying the healthcare costs.

Fracture often results in severe pain. By inhibiting the use and load of the fractured bone, pain may delay or prevent its repair, and conversely, the early use and load of the fractured bone were shown to enhance the probability of successful bone repair [12,13]. Therefore, pain management is essential, both to improve quality of life of the patients and also for the success of bone healing. Nevertheless, the commonly used analgesic therapies have limited efficacy and impose significant side effects, which may include impairment of bone repair [14,15].

The major reason why fracture pain persists a medical and social burden is the present narrow understanding of the mechanisms that generate and maintain fracture pain. Bone is known to be innervated by sensory nerve fibers, as will be discussed in the next section. However, how these nerve fibers respond to fracture and the subsequent activation of nociceptive pathways is yet largely unknown. Although some overlap may occur in the pain signaling pathways in different disorders, the knowledge of the specific pain signaling mechanisms in fractures would potentially allow the design of safe and effective targeted therapies.

In this review, the available data on bone innervation and its response to fracture is discussed, and putative mechanisms of fracture pain signaling are presented. The available therapeutic approaches to treat fracture pain and their limitations are also discussed.

2. Bone innervation

Unequivocal evidence has been provided on the intense innervation of bone, and both sympathetic and sensory nerve fibers were shown to innervate the periosteum, the mineralized bone and the bone marrow, being frequently associated with blood vessels [16–22].

Adding to the recognized role of the sympathetic nervous system in bone homeostasis, whose activation promotes bone loss [for review see 23], a regulatory role for bone metabolisms has been attributed also to the afferent sensory nerve fibers. Indeed, capsaicin-induced reduction of peripheral sensory innervation results in significant bone loss in rat [24] and in mouse [25]. This role of the sensory nervous system is further supported by the study of Fukuda et al. (2013) showing that Semaphorin 3A (Sema3A), recently implicated in the regulation of bone metabolism, exerts its regulatory function through modulating bone sensory innervation [26]. It was shown that osteoblast-specific Sema3A-deficient mice had normal bone mass, regardless of the decrease in expression of Sema3A in bone. However, a low bone mass phenotype was observed in neuron-specific Sema3A deficient mice, similar to Sema3A(−/−) mice, and in both cases this phenotype was associated with a decrease in bone sensory innervation [26]. In addition to the recently demonstrated important role of primary afferent nerve fibers in bone metabolism, bone sensory innervation is long known to be involved in processing sensory information, mainly in pain signaling.

Electrophysiological, immunohistochemistry and imaging techniques have enabled the definition of the nature and distribution of bone nerve fibers. Thinly myelinated fibers, most probably A-delta, and unmyelinated peptide-rich C-fibers have been largely reported to innervate bone [16,27–29]. These nerve fibers express neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P (SP) [16,27,29], and the majority are nerve growth factor (NGF)-sensitive expressing tropomyosin receptor kinase A (TrkA) [29]. In general, these nerve fibers are known to be responsive to noxious chemical and mechanical stimuli, and have a preponderant role in inflammatory pain signaling [30,31].

Despite some authors claiming that non-peptidergic C-fibers are mostly absent from bone, the presence of non-peptidergic C-fibers in bone has been also suggested. Ivanusic (2009) reported that 20% of the fast blue retrogradely labeled sensory neurons innervating rat tibia were isolectin B4 (IB4) positive (a marker of non-peptidergic unmyelinated neurons) [27]. The study by Castaneda-Corral el al. (2011) may also support the presence of IB4 positive nerve fibers in bone [29]. Although in this study the presence of IB4 positive fibers was not investigated, a portion of nerve fibers detected did not stain for peptides or for TrkA, so it most likely corresponds to non-peptidergic nerve fibers. Additionally, the study by Jimenez-Andrade et al. (2010) reported only a lack of Mas related G protein-coupled receptors (Mrgprd) positive fibers (Mrgprd positive nerve fibers were shown to represent 75% of the IB4 population of fibers in skin [32]), failing to investigate other non-peptidergic fibers that do not express Mrgprd. Therefore the authors did not confirm the absence of non-peptidergic nerve fibers [33]. The non-peptidergic C-fibers are sensory neurons that generally lack neuropeptide expression, bind IB4, are not sensitive to NGF, but are glial cell line-derived neurotrophic factor (GDNF)-sensitive neurons, and described to be involved in neuropathic pain [30,34,35].

Bone innervation by thickly myelinated A-beta fibers, associated with tactile or kinaesthetic sensation, has been considered absent or restricted to a few nerve fibers. Previous studies on the nerve fiber population supplying the canine tibia, report the presence of large fibers [36,37]. However, in these studies the nerve was sampled proximal to the point at which branches leave it to innervate muscle or aggregations of Pacininan corpuscles, resulting in the inclusion of nerve fibers supplying the bone-surrounding muscle or Pacininan corpusculus [36,37]. More recently, the study by Ivanusic et al. (2006) in the cat humerus supported the absence of large diameter afferent fibers in the sections of the nerve that supplies both the periosteum and the nutrient foramen [38]. Conversely, a study using retrograde tracing suggests the presence of a few large diameter neurons in bone, namely in the epiphysis of the rat tibia [27]. However, the fact that more large nerve fibers were observed following injections into the epiphysis than into medullary cavity or periosteum, supports the possibility that the visualization of large nerve fibers following injection into the epiphysis may result from the labeling of large neurons innervating the joint capsule, which is intimately associated with the epiphysis, as discussed by the authors [27]. The current lack of evidence for large neurons innervating bone, is consistent with the view that innocuous mechanosensation may be absent from the bone, or at least may not be significant. Therefore, the sensory nerve fibers that innervate bone will signal mostly noxious stimuli.

Several neurotransmitters, from neuropeptides to classical neurotransmitters, have been identified in the bone. In addition to CGRP and SP, which have been largely shown to be expressed in the population of peptidergic sensory nerve fibers [16,17,21,27,29], other neuropeptides, such as Neurokinin A [39] and Pituitary adenylate cyclase activating peptide (PACAP), were also suggested to be expressed by nerve fibers that innervate bone [40]. Vasoactive intestinal peptide (VIP) and neuropeptide Y (NPY) were shown to be expressed in bone typically by sympathetic nerve fibers [18,21,22,41]. Among the classical neurotransmitters, the expression of catecholamines, glutamate and acetylcholine has been suggested [20,29,42].

Regarding the innervation pattern of the different bone compartments, while periosteum, mineralized bone and bone marrow are all innervated by the same population of nerve fibers, the density of innervation is markedly different. The periosteum is much more densely innervated than bone marrow and mineralized bone [16,29]. In mineralized bone, the density of innervation varies also with the metabolic activity [16]. Areas with higher metabolic rate and bone turnover display the highest innervation [16], further supporting a role for bone innervation in bone metabolism.

Most of the current knowledge on bone innervation has come mainly from studies on animal models. Nevertheless, the same pattern of innervation has been suggested in humans [43,44].

3. Alterations in innervation pattern after fracture

Despite the knowledge achieved during the last decades on bone innervation, alterations in innervation patterns, related to common skeletal disorders such as osteoarthritis, bone cancer and fracture, are poorly known. What is known is that an intense nerve sprouting is associated with several skeletal diseases. Ectopic sprouting of bone nerve fibers was shown to occur in mouse models of bone cancer [45–47], and in the arthritic joints of humans and rodents the nerve fibers sprout into the articular cartilage and synovium [48–50]. Also in the case of bone fracture, an intense sprouting of fibers containing CGRP and SP, as well as containing NPY, was shown to occur in the callus area of the rat bone [51–53]. The reduction in the severity of fracture pain behavior observed in the rat as a result of neonatal capsaicin-induced depletion of peptide-rich C-fibers [54], supports the involvement of CGRP and SP containing nerve fibers in fracture pain signaling. Regarding NPY, this neuropeptide is co-released with noradrenaline by sympathetic neurons, and is barely detected in sensory neurons under normal conditions. However, NPY was described to be up-regulated in dorsal root ganglia (DRG) neurons after nerve lesion and during peripheral tissue inflammation [55–58], and suggested to be involved in pain mechanisms [56,59]. Nevertheless, it is not known to what extent the sprouting of these nerve fibers is primarily involved in signaling fracture pain. In bone cancer pain the correlation between nerve sprouting and pain intensification has been demonstrated [45,46,60], suggesting a role for the intense sprouting of nerve fibers in fracture pain signaling, but that needs further clarification.

The remarkable capacity of bone nerve fibers to undergo sprouting may be related with the expression of growth-associated protein 43 (GAP43) that is known to be involved in axonal growth, nerve sprouting and synaptic plasticity [61,62]. Actually, GAP43 expression has been shown to occur in a high number of bone nerve fibers [29]. This extensive expression of GAP43 is likely associated with the constant bone remodeling, which imposes a continuous renewal of nerve fibers. In a scenario of bone injury or disease a high basal expression of GAP43 might provide the bone nerve fibers with an increased capacity of sprouting.

Additionally, the NGF activation of TrkA expressed in nerve fibers is suggested to be involved in their sprouting following bone injury or disease. This is consistent with the anti-NGF treatment showing inhibition of the pathologic sprouting of sensory and sympathetic nerve fibers in bone cancer [46,47,60].

4. Mechanisms of fracture pain

Although different disorders have common nociceptive mechanisms, the understanding of disorder-specific pain signaling mechanisms is crucial for the development of effective targeted therapies.

Fracture repair is a dynamic process characterized by a precise temporal and spatial sequence of events that usually culminates with the reinstatement of normal bone anatomy and function [reviewed by 63,64]. In the progression of fracture repair a series of four overlapping processes is typically considered: hematoma and inflammatory response, soft callus formation, hard callus formation and bone remodeling [reviewed by 63].

Due to the highly dynamic nature of the bone repair process, different mechanisms are likely to be involved in pain signaling during the course of fracture healing.

The mechanical distortion of the periosteum has been suggested to be the major source of the immediate sharp and intense pain felt upon fracture [65,66]. It is thought that the mechanotransducers expressed by the nerve fibers that densely innervate the periosteum are activated and signal the initial fracture pain. The organization of these fibers in the periosteum was shown to be different from that in the mineralized bone and in the medullary cavity [67]. A mesh-like network organization, which was reported in mice, was suggested to facilitate the detection of the mechanical distortion of periosteum and underlying cortical bone [67]. In humans, the repositioning and stabilization of fractured bone in its normal orientation was shown to significantly attenuate pain [65,68–70]. Pain is reactivated by movement and mechanical distortion of fractured bone, supporting the mechanosensitivity role of nerve fibers that innervate bone [68–70].

After stabilization, the initial sharp and intense pain is replaced by a dull and aching pain that is suggested to result from the activation and sensitization of both A-delta and C-fibers that innervate periosteum, bone marrow and mineralized bone. In fact, Jimenez et al. (2009) reported that the neonatal capsaicin-induced intense depletion of unmyelinated C-fibers was associated with 50% reduction in the severity of pain-related behaviors [54]. The fact that significant depletion of unmyelinated C-fibers does not have a robust effect in reducing fracture pain, supports the concept that other nerve fibers, the A-delta nerve fibers, have also an important role in signaling fracture pain.

In response to injury, a set of inflammatory mediators is released by the injured tissue and inflammatory cells attracted to the damaged area, activating the nociceptive nerve fibers to produce a painful response. A broad range of algogenic factors, including kinins, amines, prostanoids, growth factors, chemokines, and cytokines, protons and ATP were identified as being part of the changed chemical environment in response to injury [71]. In the case of fracture, it is not clear if the algogenic factors are different from those of other tissue injuries. Interestingly, in sheep, the hematoma formed during the initial inflammatory phase after fracture was shown to have a cellular composition different from muscle hematoma [72]. The hematoma formed upon fracture presented lower percentage of granulocytes, higher ratio of T helper to cytotoxic T cells and increased B cell population, as compared to muscle hematoma [72]. These data suggest that the molecular mechanisms involved in fracture pain signaling during the initial steps of bone repair may be different when compared to the pain mechanisms in other disorders. In a fracture, as part of the initial inflammatory response, pro-inflammatory signals and growth factors are known to be released and interact in a precise temporal and spatial cascade, which is critical to successful bone repair [63,64,73,74]. In rodent models of fracture, the levels of cytokines such as interleukin (IL)-1, IL-6, IL-11, IL-18, and TNF-alpha were shown to be significantly enhanced during the first few days after fracture [75,76], as well as the release of transforming growth factor-beta1 (TGF-beta1), growth and differentiation factor 8 (GDF8) [77] and platelet-derived growth factor [75]. Bone morphogenetic proteins (BMP) such as BMP-2, BMP-5, and BMP-6 were also detected during the initial period after fracture [77].

Despite the increased comprehension of the molecules released during the inflammatory response in fracture, the role of these factors in pain signaling is still mostly unknown. Nevertheless, treating fracture with non-steroidal anti-inflammatory drugs (NSAIDs), therefore inhibiting prostaglandin synthesis, is known to reduce fracture pain in humans [78,79], and the administration of anti-NGF antibodies results in the reduction of pain in mouse models of fracture [80–83], supporting the involvement of these inflammatory mediators in fracture pain signaling. Amongst the broad range of inflammatory mediators released in response to fracture, a great number of molecules are certainly involved in fracture pain signaling.

Several findings support a role for different cytokines in bone pain associated with estrogen deficiency (TNF-alpha) [84], osteoarthritis (TNF-alpha and IL-1) [85][86], and bone cancer pain (IL-6) [87], and may represent important targets to be studied in order to depict fracture pain mechanisms.

Moreover, considering the intense sprouting of nerve fibers that occurs in response to fracture, in addition to the action of inflammatory mediators in nociceptors, pain in fracture may have also a neuropathic component. In other skeletal disorders, such as bone cancer and osteoarthritis, the attenuation of pain by treatment with gabapentin, a drug used to treat neuropathic pain, suggests neuropathic pain as a component of skeletal pain [88,89]. To what extent the neuropathic component contributes to fracture pain is not clear.

In fracture, the presence of allodynia, i.e. when normally innocuous stimuli are perceived as painful, and hyperalgesia, i.e. when noxious stimuli are perceived as exaggerated and prolonged pain, suggests peripheral and central sensitization. Patients with fracture are known to experience mechanical hyperalgesia and exacerbated pain when using the fractured limb (allodynia) [90,91]. In fracture pain models both allodynia, and thermal and mechanical hyperalgesia are also described [92,93].

Increased neuropeptidergic neurotransmission is one of the mechanisms putatively involved in peripheral sensitization in fracture pain, as suggested by the intense sprouting of nerve fibers expressing CRGP, SP and NPY [51–53]. Increased expression of transient receptor potential vanilloid 1 (TRPV1) in the DRG neurons that innervate the fractured femur also suggests the involvement of this ion channel in peripheral sensitization in fracture pain [94]. In fact, TRPV1 has been associated with pain in other skeletal disorders, such as osteoarthritis [95] and bone cancer pain [87].

Despite some progress, the specific molecular mechanisms of peripheral sensitization in fracture pain are still mostly unknown. Molecules such as P2X3 and P2X2/3 receptors, Nav1.8 and acid-sensing ion channel 3 (ASIC3), which have been suggested to be involved in peripheral sensitization in other skeletal pain conditions, namely bone cancer pain and estrogen deficiency-induced bone pain [96–99], can be potential targets in the study of fracture pain mechanisms.

The mechanisms of central sensitization can be very complex, involving increased membrane excitability, synaptic plasticity and decreased inhibitory transmission [reviewed by 100]. In skeletal pain these mechanisms have not been extensively addressed and the studies performed have focused mainly in disorders other than fracture, such as bone cancer pain and osteoarthritis. Activation of microglia in the spinal cord was suggested to underlie central sensitization in models of bone cancer pain and osteoarthritis [101–103]. Increased spinal activity of P2X7 receptor [104] and PI3K/pAKT pathway [105], as well as changes in glutamate receptors [106,107] were also suggested as important signaling mechanisms in bone cancer pain models, and in rodent models of osteoarthritis, increased expression of pro-inflammatory cytokines and chemokines [108] and enhanced neuropeptidergic signaling in the spinal cord were suggested to be involved in central sensitization [109,110]. To our knowledge, the mechanisms of central sensitization after fracture have only been addressed when a state of chronic pain is established after fracture healing; this will be discussed in the next section. The mechanisms that drive central sensitization in proper fracture healing, and in which central sensitization will be reversed with bone repair, are remarkably unknown.

It remains challenging to explore the specific mechanisms that generate and maintain fracture pain throughout fracture repair. Such knowledge would significantly extend our ability to design effective and safe mechanism-based therapies to treat fracture pain.

5. Establishment of chronic pain after fracture

When fracture does not produce severe nerve injury and heals properly, pain decreases with soft callus formation and bone bridging, vanishing completely with bone repair [92,93]. In cases of inadequate fracture healing, for instance due to bone metabolic disorders such as osteoporosis, a state of chronic pain develop. An exuberant sprouting of sensory and sympathetic nerve fibers and the formation of neuroma-like structures, are suggested to be involved in the establishment of chronic pain in bones with impaired healing [111]. In other cases, despite fracture repair, alterations in peripheral and central nervous system responsible for pain sensitization may persist, leading to a state of chronic pain, known as Complex Regional Pain Syndrome (CRPS). CRPS is a severe chronic pain condition that affects mostly limbs and is characterized by the presence of pain in combination with other sensory, autonomic, motor and trophic disorders [112,113]. Generally, CRPS develops after minor or moderated tissue injury, such as a fracture, sprain or surgery, and fracture is its most common precipitating event [114].

CRPS seems to be associated with an aberrant host response to the tissue injury. Multiple mechanisms are known to be involved, including altered cutaneous innervation, changed sympathetic activity, peripheral and central sensitization, increased levels of local and systemic inflammatory cytokines, and decreased systemic levels of anti-inflammatory cytokines [112,115]. In an initial stage of the disorder, the affected extremity is usually severely painful, with allodynia, and mechanical and thermal hyperalgesia commonly present [116]. The voluntary motor control may be reduced with disease progression [116]. Sensory disturbance may also be installed, with patients showing allodynia and hyperalgesia in combination with loss of sensitivity to touch and to small changes in temperature [116].

Concerning with the development of CRPS specifically after fracture, several animal studies have explored the underlying mechanisms. In the rat tibia fracture model of CRPS, the expression of IL-1beta, IL-6, TNF-alpha, NGF was up-regulated in the hindpaw skin, and inhibition of TNF-alpha, IL-1beta and NGF signaling was shown to prevent allodynia, supporting a role for inflammatory mediators in the development of CRPS [117–119]. Both in rat and mouse fracture models of CRPS, levels of CGRP and SP were described to be increased in the sciatic nerve [118,120], and suggested to underlie the up-regulation of expression of inflammatory mediators, such as IL-1beta, TNF-alpha and NGF [119,121]. Expression of Fos, neuropeptides (SP and CGRP) and inflammatory mediators (TNF-alpha, IL-1, IL-6, CCL2, NGF) was found to be enhanced in the spinal cord of the rat tibia fracture model of CRPS [118,122], and increased neuropeptidergic signaling was suggested to underlie the upregulation of inflammatory mediators, contributing to central sensitization [122].

Overall, most of the studies on pain signaling mechanisms after fracture, in CRPS models, report an increase of inflammatory mediators and neuropeptide signaling upregulation that is suggested to facilitate neurogenic inflammation. Moreover, the inhibition of inflammatory mediators and neuropeptides signaling has been shown to result in the reduction of CRPS associated pain.

6. Therapeutic options for fracture pain management

Treating pain associated with fracture is essential to patient wellbeing, but it is also of crucial importance for proper bone healing. Currently, the available therapeutic options to treat bone pain are very limited. The treatment of bone pain, whether malignant or non-malignant in origin, is mostly based on the World Health Organization's three-step analgesic ladder for cancer pain. As reviewed by Ringe and Body (2007), the first therapeutic option consists of analgesics administration, such as paracetamol and NSAIDs; if this is not effective, the therapeutics is complemented with a weak opiate, and if pain persists a stronger opiate is prescribed. Adjuvant agents, such as tricyclic antidepressant or membrane-stabilizing agent may be concomitantly used during each of the described therapeutic steps [123,124]. The treatment of fracture pain is not an exception and also follows this approach. After fracture, pain is firstly reduced by fracture stabilization and the subsequent treatment is based on the use of NSAIDs and opiates [124–

126]. The significant side effects imposed, which in fracture pain may include impaired bone healing, are a major concern of this limited approach.

NSAIDs act by inhibiting cyclo-oxygenase (COX)-1 and COX-2, and result in the inhibition of prostaglandins synthesis. NSAIDs are commonly used to treat musculoskeletal pain [127–130], however, these drugs present severe side effects, including increased risk of gastrointestinal and cardiovascular adverse events [128,131,132]. The more recent class of NSAIDs, the specific COX-2 inhibitors, has been reported to be as effective as the classical NSAIDs and to have less gastrointestinal and bleeding effects, although the risk of cardiovascular adverse events has been suggested [133–135]. Importantly, there are animal studies reporting an association between both classes of NSAIDs and an abnormal bone healing process [14,136,137].

In response to injury, COX-2 is upregulated increasing the expression of prostaglandins that will stimulate the release of inflammatory mediators and regulate the activity of osteoblasts and osteoclasts [73]. Knowing the central role of inflammatory mediators, and osteoblasts and osteoclasts in bone repair process, treating pain with NSAIDs is likely to compromise the success of fracture repair. In fracture rodent models, increased bone nonunion rates and decreased bone strength support the correlation between NSAIDs and abnormal fracture healing [14,136–138]. Moreover, the mutation of COX-2 in mouse is known to result in impaired fracture healing [139]. In humans, despite having been suggested [15,140], the association between NSAIDs and impaired fracture healing is not clear [141,142]. Differences in drug used, dose and duration of administration between studies have led to inconclusive results [142–144]. Therefore, the precise effects of NSAIDS on fracture healing need to be further clarified.

Opiates are a very effective class of analgesic drugs, and are commonly used to control severe musculoskeletal pain [125,145]. However, a variety of central nervous system side effects are well known. Among the main concerns are the development of tolerance and dependence after long-term use, but opiates also cause somnolence, agitation and dizziness [145–147], which may reduce mobility and decrease the ability to participate in the rehabilitation process, therefore indirectly impairing bone healing. Direct effects of opiates in bone healing are not widely explored yet [148].

Although NSAIDs and opiates are essential components of currently available therapeutics to manage fracture pain, their significant side effects, namely those regarding the impact in fracture healing, highlight the need of novel effective and safe therapies.

Bisphosphonates, a class of drugs primarily used to prevent bone mass loss, have been suggested as a therapeutic option for bone pain. Bisphosphonates were shown to effectively reduce pain in disorders associated with increased bone turnover, such as metastatic bone diseases and osteoporosis [149–152]. Importantly, these drugs reduce osteoclastic activity [reviewed by 153]. So, in a fracture repair scenario, where a precise sequence of cellular and molecular events is required, bisphosphonates can deregulate the required balance, invalidating their use as an option to treat fracture pain.

Increasing attention has been given to the Anti-NGF approach in fracture pain management. The NGF released in response to injury will activate TrkA in sensory nerves, increasing neuropeptidergic signaling, leading to an upregulation of capsaicin receptor (TRPV1) expression and brain-derived neurotrophic factor (BDNF), molecules that will modulate peripheral and central pain mechanisms [reviewed by 154]. Blocking NGF/TrkA signaling seems to be a putative effective strategy to attenuate fracture pain, since, as described in Section 2, bone is densely innervated by sensory nerve fibers expressing TrkA.

Evidence from preclinical and clinical studies confirms the analgesic effect of anti-NGF therapy in pain conditions such as bone cancer pain, low back pain and osteoarthritis [155–160]. Notably, the administration of anti-NGF antibody has also been shown to result in a significant reduction of pain-related behavior in rodent fracture pain models [80–83]. Moreover, this approach has been suggested to not modify bone biomechanical properties or histomorphometric indices of bone healing, therefore not impairing bone repair [80–83].

Despite evidence of its efficacy in several pain conditions, safety concerns on anti-NGF therapies have been raised. In addition to being involved in signaling pain, NGF is essential for the proliferation, differentiation and survival of sympathetic and primary sensory neurons [161,162] and thus, the use of anti-NGF agents may cause or worsen peripheral neuropathies. A meta-analysis by Leite et al. (2014) emphasizes the increased risk of neurological adverse effects, including headache, hyperesthesia, abnormal peripheral sensation, and dizziness [163]. Moreover, the high incidence of rapidly progressive osteoarthritis/osteonecrosis in patients receiving anti-NGF treatment led the US Food and Drug Administration to put on hold anti-NGF studies in 2010 [164]. The aetiology of this side effect is still poorly understood. However, in 2012, after a debate on the benefit/risk of this therapeutic approach, the US Food and Drug Administration revised its former decision and stated that there was a role for the development of anti-NGF therapies for painful conditions that are refractory to currently available therapies, such as bone cancer pain, interstitial cystitis and pancreatitis [164] In addition, the implementation of new safety procedures was imposed in order to avoid new cases of joint destruction [164]. More advanced experimental studies are required to improve the current knowledge on the pathophysiology of anti-NGF therapy. Also, it should be stressed that the analgesic effects of anti-NGF approach have been only investigated after systemic administration, and local administration would justify further attention to possibly overcome the adverse effects of systemic anti-NGF administration.

Finally, the definition of the degree of pain reduction should be considered in the management of skeletal pain. The complete elimination of pain sensation in fracture conditions can lead to the inappropriate loading or overuse of affected bone, preventing the normal progression of bone repair. Therefore, additional measures may have to be considered to prevent this situation.

7. Conclusion

The increased knowledge of bone innervation and its response to fracture have been contributing to the understanding of fracture pain mechanisms. However, there is still much to be uncovered. Elucidation of the mechanisms of peripheral and central sensitization would allow the design of mechanisms-based therapies to effectively manage fracture pain, surpassing drawbacks of the current available therapies.

Conflict of interest

The authors declare no conflict of interest.

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