Journal of Anesthesia (2019) 33:131–139
https://doi.org/10.1007/s00540-018-2579-4

INVITED REVIEW ARTICLE

Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain

Megumi Matsuda[1,2] · **Yul Huh**[1] · **Ru-Rong Ji**[1]

Received: 20 September 2018 / Accepted: 26 October 2018 / Published online: 17 November 2018

Abstract

Inflammation is the body's response to injury and infection, involving a complex biological response of the somatosensory, immune, autonomic, and vascular systems. Inflammatory mediators such as prostaglandin, proinflammatory cytokines, and chemokines induce pain via direct activation of nociceptors, the primary sensory neurons that detect noxious stimuli. Neurogenic inflammation is triggered by nerve activation and results in neuropeptide release and rapid plasma extravasation and edema, contributing to pain conditions such as headache. Neuroinflammation is a localized inflammation in the peripheral nervous system (PNS) and central nervous system (CNS). A characteristic feature of neuroinflammation is the activation of glial cells in dorsal root ganglia, spinal cord, and brain which leads to the production of proinflammatory cytokines and chemokines in the PNS and CNS that drives peripheral sensitization and central sensitization. Here, we discuss the distinct roles of inflammation, neurogenic inflammation, and neuroinflammation in the regulation of different types of pain conditions, with a special focus on neuroinflammation in postoperative pain and opioid-induced hyperalgesia.

Keywords Pain · Inflammation · Neurogenic inflammation · Neuroinflammation

Introduction

The biological significance of acute pain is to avoid potential damage and protect wounded tissue. In contrast, chronic pain is maladaptive and has no beneficial biological significance. Chronic pain has long been recognized as a pain state that continues beyond normal healing time, thus lacking the acute warning function of physiological nociception. According to the International Classification of Diseases (ICD), chronic pain is defined as pain that persists or recurs for more than 3 months and has been further delineated by the IASP Task Force for the Classification of Chronic Pain (2016).

Chronic pain is a major health concern in the world. It is estimated that chronic pain affects one in three Americans and with an annual cost over $600 billion dollars [1, 2]. As shown in Table 1, the incidence of chronic pain in Japan ranges from 13.4 to 47% [3–10]. The largest internet survey of 41,597 Japanese residents by Yabuki et al. reported a chronic pain (> 3 months) incidence of 22.5% [6].

In particular, major surgeries result in high incidence of chronic postsurgical pain (CPSP). The prevalence of CPSP occurs in 20–50% patients after thoracic and breast surgeries (thoracotomies and mastectomies) and up to 80% of patients following amputations, with 5–10% patients suffering from severe chronic pain [11–13]. The prevalence of CPSP in Japan at 3 and 6 months is 18% and 12% after lung surgery and 49% and 33% after total knee arthroplasty [14].

Chronic pain is maladaptive and characterized by spontaneous pain (e.g., burning) as well as evoked pain in response to noxious (hyperalgesia) or non-noxious (allodynia) stimuli. It is well understood in the pain research community that neuronal and synaptic plasticity, i.e., neural plasticity in pain coding pathways and circuits results in chronic pain. Neuronal plasticity occurs in primary sensory neurons of dorsal root ganglia (DRG) and trigeminal ganglia (peripheral

✉ Megumi Matsuda
mmatsuda@koto.kpu-m.ac.jp

✉ Ru-Rong Ji
ru-rong.ji@duke.edu

[1] Center for Translational Pain Medicine, Department of Anesthesiology, Duke University Medical Center, 3 Genome CT, MSRB3 Room 6148, Durham, NC 27710, USA

[2] Research Unit for the Neurobiology of Pain, Department of Anesthesiology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Table 1 Chronic pain prevalence in Japan

First author	Year	Survey method	Age (years)	Participants (response rate)	Duration of pain (months)	Prevalence (%)
Hattori [3]	2004	Internet	≥ 18	18,300 (72.2%)	6	13.4
Matsudaira [4]	2011	Internet	20–80	20,044 (20.1%)	3	22.9
Nakamura [5]	2011	Postal	≥ 18	11,507 (60%)	6	15.4
Yabuki [6]	2012	Internet	≥ 20	41,597 (unknown)	3	22.5
Ogawa [7]	2012	Internet	20–69	20,000 (unknown)	3	26.4
Shibata [8]	2014	Interview	≥ 40	927 (46%)	6	47
Inoue [9]	2015	Postal	≥ 20	2628 (43.8%)	6	39.3
Inoue [10]	2017	Postal	≥ 20	5437 (54.4%)	6	16.6

sensitization) as well as in pain-processing neurons in the spinal cord and brain (central sensitization) [15, 16].

Inflammation and pain

A complex interplay between various biological responses of the immune system, the autonomic nervous system, vascular regulation, and the central and peripheral nervous systems in response to the insults of tissue injury, pathogens, and irritants comprise the sensation of pain by the body. Pain can serve a vital protective role for an organism, as is the case with acute inflammation that results in the perception of pain, leading to avoidance of harmful stimulus and encouraging healing of damaged tissue [17]. Inflammatory mediators, produced during inflammation, evokes pain via direct activation and sensitization of nociceptors [18, 19]. Nociceptors are a subset of primary afferent neurons, with cell bodies located in the DRG and trigeminal ganglia, that respond to tissue injury, and are made up of both unmyelinated C-fibers and myelinated Aδ-fibers innervating skin, muscle, joint, and visceral organs. These tissue injury sensitive neurons signal through the activation or sensitization of G-protein coupled receptors (GPCRs), ionotropic receptors, and tyrosine kinase receptors located on nerve terminals and cell bodies. These receptors are directly bound and activated by a variety of inflammatory mediators, including but not restricted to, bradykinin, prostaglandins (e.g., PGE2), H^+, ATP, nerve growth factor (NGF), as well as proinflammatory cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and CCL2 [17, 19–22].

The phenomenon of peripheral sensitization, which is marked by a state of hypersensitivity and hyperexcitability of nociceptors as a result of tissue injury and inflammation, is caused by the activation of a varied collection of ion channels including the transient receptor potential ion channels (i.e., TRPA1, TRPV1, and TRPV4) [23, 24], sodium channels (i.e., Nav1.7, Nav1.8, and Nav1.9) [25, 26], and mechanosensitive piezo ion channels [27]. Protein kinases including MAP kinases, protein kinase A (PKA), and protein kinase C (PKC) are critical activating links in the receptor signaling pathways of nociceptors, leading to peripheral sensitization induction and maintenance [28–31]. It has been found that peripheral sensitization is marked by increased TRPV1 activity in response to TNF [32] and increased Nav1.8 activity in response to IL-1β [33], with both of these increased ion channel responses resulting from p38 MAP kinase activation in DRG neurons [34–36]. Continued elevated TRPV1 expression maintains the state of peripheral sensitization and consequently transition from acute to chronic pain [34, 37, 38]. In addition to inflammatory and neuropathic pain [34, 39], activation of p38 MAP kinase in DRG neurons with C- and Aδ-fibers also contributes to pain hypersensitivity after plantar incision [40].

Nociceptor priming or hyperalgesic priming is a unique form of peripheral sensitization [41]. The inflammatory mediator PGE2 normally produces a transient hyperalgesia for hours in naïve animals. However, when preceded by a prior insult (e.g., IL-6 or carrageenan), a peripheral injection of PGE2 results in sustained hyperalgesia for weeks [41]. Interestingly, PGE2 also produces long-lasting hyperalgesia after priming with plantar incision [36]. This sustained post-incisional nociception is mediated by an upregulation of exchange protein directly activated by cyclic adenosine monophosphate (EPAC) in DRG. Of note, treatment with FR167653 [42, 43], a selective p38 MAP kinase inhibitor, prior to the incision, prevented the development of nociceptor priming and incision-induced EPAC expression in DRG neurons, presumably nociceptors [36].

Interestingly, nociceptors and immune cells are involved in neuroimmune communication involving a common repertoire of inflammatory mediators including cytokines, chemokines, and TLRs [44, 45]. Thus, in the context of inflammation and pain, neuroimmune interactions enable the modulation of both nociceptor and immune response to injury by regulating both resident immune cells as well as recruitment of immune cell populations to the area of local inflammation, primary afferents, and DRG [46]. A particular

example is the role of neuronal TLR signaling in regulating macrophage activation in the vicinity of DRG by producing CCL2 chemokine in nociceptors [44, 47]. In 2010, Amaya and coworkers first demonstrated that an induction of high mobility group box-1 (HMGB-1), an endogenous ligand of TLR2/4, in DRG neurons occurs after peripheral nerve injury, and this process is critical for the induction of neuropathic pain [48].

It is important to point out that acute inflammation not only induces pain but also promotes the resolution of pain by producing specialized pro-resolving mediators (SPMs), including resolvins (RvD1, RvD2, RvD5, RvE1), protectin or neuroprotectin (PD1/NPD1), and maresin (MaR1) derived from fish oil. SPMs, produced during the resolution phase of inflammation, exhibit potent anti-inflammatory actions in various animal models of inflammation [49, 50]. Notably, SPMs are also potent analgesics that inhibit and resolve inflammatory pain and postoperative pain [51, 52].

Peripheral inflammation also results in hyperactivity of the central nervous system (CNS), including the spinal cord and brain as well as primary afferent central terminals in the spinal cord and trigeminal nucleus. The CNS exhibits increases in the production and release of neurotransmitters and/or neuromodulators involved in inflammation including glutamate, the neuropeptides substance P and CGRP, as well as the neurotrophic factor BDNF, when persistently activated by inflammatory input from peripheral nociceptors [39, 53]. Persistent nociceptive input in turn results in the development of central sensitization, marked by the hyperactivity and hyperexcitability of neurons in the brain and spinal cord [15, 16]. Furthermore, there is particular involvement of postsynaptic glutamate NMDA receptors and insertion of AMPA receptors in the plasma membrane, as well as activation of ERK in postsynaptic neurons [54], to initiate and maintain central sensitization [15, 16]. Loss of inhibitory control (e.g., inhibitory synaptic transmission [55]) and inhibitory signal molecules (e.g., β−αρρεστιν−2 [56]) is sufficient to drive central sensitization and pain hypersensitivity.

Neurogenic inflammation and pain

Neurogenic inflammation results from nociceptor activation and can be experimentally caused with immediate onset by intradermal administration of capsaicin, which activates TRPV1, or mustard oil, which activates TRPA1 [57]. The activated nociceptors, notably C-fibers, release a host of neuropeptides such as substance P, CGRP, and prostanoids. Following the activation of nociceptors, rapid plasma extravasation and edema occurs at a timescale faster than that of immune cell infiltration. Among clinical conditions, neurogenic inflammation has been found to be particularly involved in inflammatory diseases including asthma and psoriasis [18]. Additionally, neurogenic inflammation is a major component of pain caused by migraines as well as complex regional pain syndrome (CRPS) due to bone fracture [58]. Although the ablation of nociceptors can decrease neurogenic inflammation, it must be noted that nociceptors can play a modulatory role that can be beneficial in other scenarios, for example the release of CGRP by nociceptors which has been found to regulate inflammation in bacterial infections [59, 60].

The generation of neurogenic inflammation is not only limited to activation of peripheral C-fibers but can also be caused by local inflammation events or even by CNS activation of primary afferents in the case of dorsal root reflex resulting from orthograde or anterograde neuronal activation [61]. The CNS itself can also be subject to neurogenic inflammation following neuroinflammation events in the brain or spinal cord [18, 61].

Neuroinflammation and pain

Neuroinflammation is a localized form of inflammation occurring in both the PNS and CNS [17]. Four features of neuroinflammation include increased vascular permeability, leukocyte infiltration, glial cell activation, and increased production of inflammatory mediators such as cytokines and chemokines [17]. In the state of neuroinflammation, the blood brain barrier is subject to an increased level of permeability, exposing the CNS to increased infiltration by peripheral immune cells. Accordingly, neuroinflammation is increasingly being implicated in chronic pain disorders including postsurgical pain following major surgeries such as amputation, thoracotomy, and mastectomy, and postoperative complications such as delirium [18, 62].

Although chronic pain is observed as a condition that continues beyond the resolution of observable clinical signs and symptoms of inflammation, neuroinflammation actually maintains a close association with chronic pain states and may be responsible for the mediation and continuation of pain in human patients [63]. Of note, chronic pain is correlated differently with inflammation and neuroinflammation. Chronic neuroinflammation has been observed in patients of HIV neuropathy and also in patients with fibromyalgia [63, 64]. The involvement of different neuroinflammatory mediators in modulating pain sensitivity in the pain neurocircuitry will be a particularly interesting area of inquiry.

Glial activation and neuroinflammation after surgery and opioid treatment

Peripheral glia [i.e., Schwann cells and satellite glial cells (SGCs)] and central glia (i.e., microglia, astrocytes and oligodendrocytes) are activated during neuroinflammation [65,

66]. In DRG, nerve injury not only causes neuronal changes leading to peripheral sensitization but also results in activation of SGCs, which contributes to peripheral neuroinflammation and neuropathic pain via SGC–neuron interactions (Fig. 1) [65, 67, 68]. Notably, opioids produce not only analgesia but also paradoxical hyperalgesia, which could be conveyed by SGCs. Strikingly, a single intraperitoneal injection of morphine is sufficient to activate SGCs [69]. This activation requires the upregulation of matrix metalloprotease-9 (MMP-9) in DRG neurons, which causes IL-1β cleavage and release to activate SGCs [69]. As a result, opioid analgesia is suppressed by MMP-9/IL-1β-mediated SGC activation but enhanced in mice lacking *Mmp9* [69, 70]. Plantar incision produced a rapid activation (within 1 h) of ERK not only in large-size DRG neurons but also in surrounding SGCs. Blocking the coupling of neuron-SGC with the gap junction blocker carbenoxolone inhibited neuronal ERK activation and postsurgical pain [71], supporting an essential role of neuron-SGC interactions in the initiation of postsurgical pain. It remains to be investigated if MMP-9 and IL-1β are involved in ERK activation in SGCs after plantar incision.

With regard to the central glia, which is the focus of the majority of glial studies on pain, the mediators and actions produced by these cells serve major modulatory roles in the processes of synaptic plasticity and central sensitization [18]. Notably, the phenomenon of glial activation has emerged in recent literature as a potent mechanism in chronic pain, and the resulting dysfunction of glia in chronic pain has been referred to as "gliopathy" [65]. Nerve injury results in remarkable microgliosis and astrogliosis in the spinal cord [65, 72, 73]. Spinal microgliosis was also reported after plantar incision [43]. Multiple receptors, such as ATP receptors (e.g., P2X4, P2X7, P2Y12) [73–75], chemokine receptors (e.g., CX3CR1, CXCR5) [76, 77], and Toll-like receptors (e.g., TLR4) [78], along with proteases such as matrix metalloproteases (MMP-9 and MMP-2) and cathepsin S (CatS) [79–81] have been shown to regulate glial activation and neuropathic pain.

In particular, following nerve injury, surgery (e.g., plantar incision), and chronic opioid exposure, p38 MAP kinase is not only activated in DRG neurons during peripheral sensitization but also activated in spinal microglia during central sensitization [43, 75, 82, 83]. Thus, activation of p38 MAP kinase plays an important role in neuropathic pain, postsurgical pain, and opioid tolerance via regulating neuroinflammation [84]. p38 MAP kinase regulates microglial secretion of TNF, IL-1β, αvδ BΔNΦ, all of which are powerful regulators of central sensitization [85, 86] (Fig. 2). Interestingly, blockade of both A-fibers and C-fibers together, but not C-fibers alone, can prevent microglial activation in the spinal cord after nerve injury [87]. Consistently, blocking large A-beta fibers but not small C-fibers alleviated mechanical allodynia, a cardinal feature of chronic pain after chemotherapy and nerve injury [88]. Nerve injury, surgery, and chronic opioid exposure also activate spinal cord astrocytes, and persistent astrocyte activation maintains neuropathic pain via sustained neuroinflammation [65, 89]. Mechanistically, astrocyte-produced chemokines such as CCL2 and CXCL1,

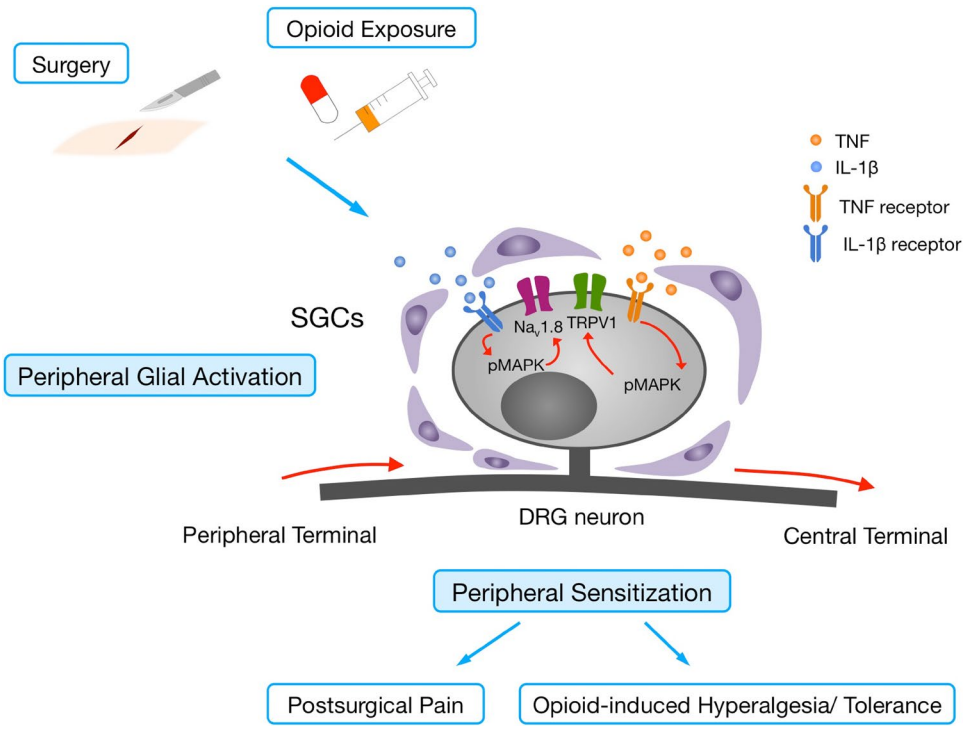

Fig. 1 Schematic illustration of peripheral sensitization induced by peripheral glial activation and neuroinflammation in dorsal root ganglia (DRG) following surgeries and opioid exposure. Activation of peripheral glia (i.e., SGCs: satellite glial cells) by surgery and/or opioid treatment results in secretion of glial mediators such as TNF and IL-1β, leading to peripheral sensitization, postsurgical pain, and opioid-induced hyperalgesia and tolerance

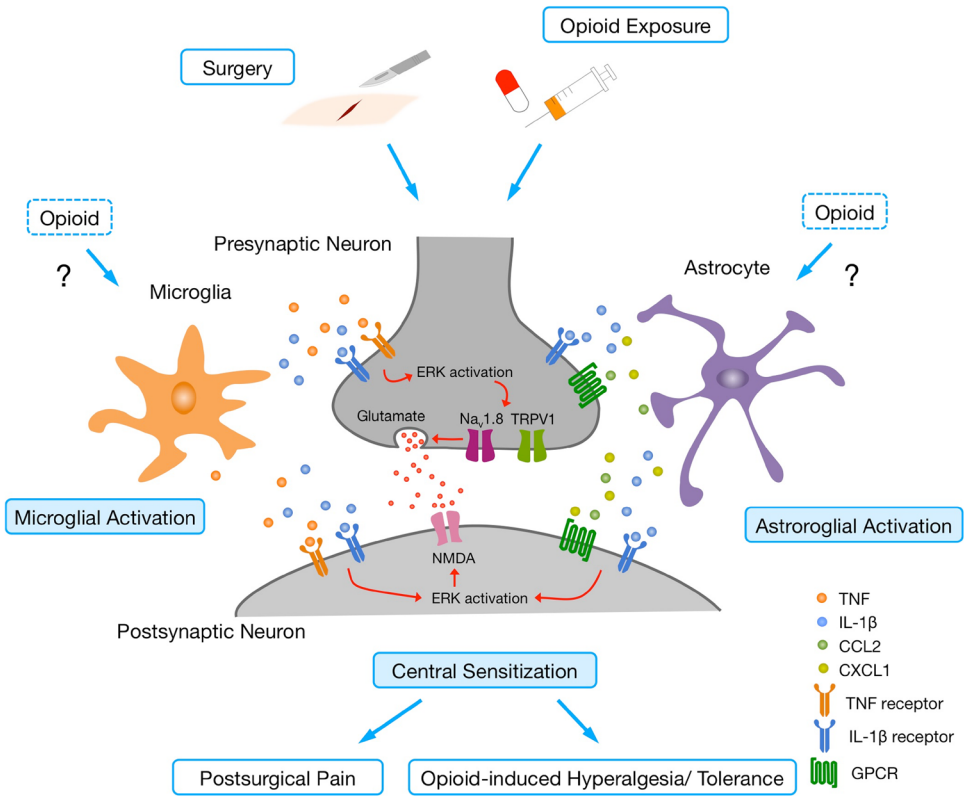

Fig. 2 Schematic illustration of central sensitization induced by glial activation and neuroinflammation in the spinal cord following surgery and/or opioid exposure. Activation of central glia (microglia and astrocytes) in the spinal cord by surgery and/or opioids treatment results in secretion of glial mediators including TNF, IL-1β, CCL2, CXCL1, and BDNF. These factors can act as neuromodulators to induce central sensitization via the modulation of excitatory and inhibitory synaptic transmission. Central sensitization is a driving force of postsurgical pain as well as opioid-induced hyperalgesia and tolerance

as well as cytokines (e.g., IL-1β), powerfully regulate central sensitization [90, 91] (Fig. 2).

Surgical incisions and resulting nerve injury have been shown to cause increased expression of COX-1 in spinal glial cells which can lead to postsurgical pain and neuropathic pain development following a surgery [92, 93]. P2X7 receptors and spinal glial cells also contribute to the development of chronic postsurgical pain induced by incision and retraction of skin and muscle tissue [94]. Furthermore, discrepancies between inflammation in peripheral tissues and central neuroinflammation in acute versus chronic pain support the notion that central neuroinflammation maintains chronic pain states [18, 95]. This was suggested from a study of a rat model of complex regional pain syndrome (CRPS), where levels of IL-1β were elevated in peripheral and spinal samples at the acute phase 4-week time point, but at the chronic phase 16-week time point only spinal levels of IL-1β remain elevated. Furthermore, the efficacy of anakinra treatment to antagonize IL-1 was delineated along the same peripheral versus central compartments, as peripheral anakinra treatment was effective at inhibiting nociceptive behavior measurements at only the 4-week time point, whereas intrathecal anakinra treatment was able to inhibit nociception at both the 4-week and 16-week time points [96]. Thus, neuroinflammation, especially central neuroinflammation, plays an essential role in maintaining chronic pain. Notably, central neuropathic pain after spinal cord injury is associated with peripheral sensitization in DRG neurons [97]. It was recently proposed that central neuroinflammation and central sensitization could maintain chronic pain in part by driving peripheral sensitization via diffusion and retrograde signaling [18].

Clinical significance and future perspectives

As detailed in the preceding sections, there are different types of inflammation, namely classic inflammation (referred to as "inflammation" in this review), neurogenic inflammation, and neuroinflammation. Although all three types of inflammation play active roles in pain and anti-inflammatory drugs are partially effective in treating acute pain and pain, it is important to make distinctions among different types of inflammation from a therapeutic perspective. For example, inhibiting neurogenic inflammation with nerve block such as by Botox (botulinum neurotoxin A) or anti-CGRP antibody show great efficacy in reducing bacterial infection, inflammatory pain, and headache [57, 98–100]. Given the important role of central neuroinflammation in maintaining chronic pain, delivery of anti-inflammatory drugs to the CNS is critical. Thus, intrathecal but not peripheral administration of anakinra, an FDA-approved anti-IL-1β treatment, can alleviate CPSP in rodents in the late phase (16 weeks) after bone fracture [96].

Neuroinflammation resulting from neuroglial and neuroimmune interactions not only serves as a driving force for chronic pain, but is also implicated in other neurological and psychiatric diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism, major depression, and schizophrenia [17], as well as in cognitive deficits after major surgeries [62]. Chronic pain is commonly associated with depression, anxiety, sleep disorders, and cognitive decline, which are clinical sequelae of particular concern to the growing aging population which has increasingly high prevalence of chronic pain. Neuroinflammation and astrocyte reactivity is also associated with chronic pain in postmortem human spinal cord samples [63]. Glial activation can further be detected in patients with chronic low back pain using positron emission tomography (PET) imaging [101]. Thus, targeting excessive neuroinflammation will be a promising approach to alleviate chronic pain and control the progression of neurological and psychiatric diseases. Notably, there is ongoing opioid crisis in the United States with hundreds of Americans dying from opioid overdoses every day [102]. Therefore, the development of effective non-opioid treatments for the prevention and resolution of neuroinflammation and postoperative pain is of utmost urgency. Finally, it is worthy to mention that non-pharmacological alternative treatments, such as cellular therapy with bone marrow stem cells show promising long-term pain relief via powerful control of neuroinflammation [103–105]. Autologous conditioned serum and platelet-rich plasma contain high levels of anti-inflammatory cytokines and produce relief in patients with knee osteoarthritis [106–108]. Neuromodulation via spinal cord stimulation and electroacupuncture also demonstrate the ability to control neuroinflammation for pain relief [18, 109, 110]. Further studies are warranted in the future to investigate how these alternative strategies control CPSP and neuroinflammation after surgery.

Acknowledgements This study is supported in part by Grants of R01DE17794, R01DE22743, R0187988 to RRJ from the National Institutes of Health, Bethesda, USA.

Compliance with ethical standards

Conflict of interest The authors have no competing financial interests in this study.

References

1. Pizzo PA, Clark NM. Alleviating suffering 101—pain relief in the United States. N Engl J Med. 2012;366:197–9.
2. Gereau RW, Sluka KA, Maixner W, Savage SR, Price TJ, Murinson BB, Sullivan MD, Fillingim RB. A pain research agenda for the 21st century. J Pain. 2014;15:1203–14.
3. Hattori STN. The clinical perspective on chronic pain management in Japan. Pain Clin. 2004;25:1541–51.
4. Matsudaira KTK. Prevalence and characteristics of chronic pain in the general Japanese population. Pain Clin. 2011;32:1345–56 **(Japanese)**.
5. Nakamura M, Nishiwaki Y, Ushida T, Toyama Y. Prevalence and characteristics of chronic musculoskeletal pain in Japan. J Orthop Sci. 2011;16:424–32.
6. Yabuki SUT. A nationwide survey of chronic pain sufferers in Japan. J Jpn Clin Orthop Assoc. 2012;47:127–34 **(Japanese)**.
7. Ogawa SIM. A large-scale survey on chronic pain and neuropathic pain in Japan. J Jpn Clin Orthop Assoc. 2012;47:565–74.
8. Shibata MNT. Alexithymia is associated with greater risk of chronic pain and negative affect and with lower life satisfaction in a general population: the Hisayama Study. PLoS One. 2014;9:e90984.
9. Inoue SKF. Chronic pain in the japanese community—prevalence, characteristics and impact on quality of life. PLoS One. 2015;10:e0129262.
10. Inoue STT. The prevalence and impact of chronic neuropathic pain on daily and social life: a nationwide study in a Japanese population. Eur J Pain (London England). 2017;21:727–37.
11. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618–25.
12. Karmakar MK, Ho AM. Postthoracotomy pain syndrome. Thorac Surg Clin. 2004;14:345–52.
13. Macrae WA. Chronic pain after surgery. Br J Anaesth. 2001;87:88–98.
14. Sugiyama Y, Iida H, Amaya F, Matsuo K, Matsuoka Y, Kojima K, Matsuno F, Hamaguchi T, Iseki M, Yamaguchi K, Takahashi Y, Hara A, Sugasawa Y, Kawamata M, Tanaka S, Inagaki Y, Otsuki A, Yamazaki M, Ito H. Prevalence of chronic postsurgical pain after thoracotomy and total knee arthroplasty: a retrospective multicenter study in Japan (Japanese Study Group of Subacute Postoperative Pain). J Anesth. 2018;32:434–8.
15. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26:696–705.
16. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10:895–926.
17. Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov. 2014;13:533–48.
18. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology. 2018;129:343–66.
19. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413:203–10.
20. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010;16:1248–57.
21. White FA, Bhangoo SK, Miller RJ. Chemokines: integrators of pain and inflammation. Nat Rev Drug Discov. 2005;4:834–44.
22. Amaya F, Izumi Y, Matsuda M, Sasaki M. Tissue injury and related mediators of pain exacerbation. Curr Neuropharmacol. 2013;11:592–7.
23. Moore C, Gupta R, Jordt SE, Chen Y, Liedtke WB. Regulation of pain and itch by TRP channels. Neurosci Bull. 2018;34:120–42.
24. Bautista DM, Jordt SE, Nikai T, Tsuruda PR, Read AJ, Poblete J, Yamoah EN, Basbaum AI, Julius D. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. Cell. 2006;124:1269–82.
25. Amaya F, Decosterd I, Samad TA, Plumpton C, Tate S, Mannion RJ, Costigan M, Woolf CJ. Diversity of expression of the sensory neuron-specific TTX-resistant voltage-gated sodium ion channels SNS and SNS2. Mol Cell Neurosci. 2000;15:331–42.
26. Waxman SG, Dib-Hajj S, Cummins TR, Black JA. Sodium channels and pain. Proc Natl Acad Sci USA. 1999;96:7635–9.

27. Eijkelkamp N, Linley JE, Torres JM, Bee L, Dickenson AH, Gringhuis M, Minett MS, Hong GS, Lee E, Oh U, Ishikawa Y, Zwartkuis FJ, Cox JJ, Wood JN. A role for Piezo2 in EPAC1-dependent mechanical allodynia. Nat Commun. 2013;4:1682.
28. Ji RR, Gereau RW, Malcangio M, Strichartz GR. MAP kinase and pain. Brain Res Rev. 2009;60:135–48.
29. Obata K, Noguchi K. MAPK activation in nociceptive neurons and pain hypersensitivity. Life Sci. 2004;74:2643–53.
30. Gold MS, Levine JD, Correa AM. Modulation of TTX-R INa by PKC and PKA and their role in PGE2-induced sensitization of rat sensory neurons in vitro. J Neurosci. 1998;18:10345–55.
31. Aley KO, Levine JD. Role of protein kinase A in the maintenance of inflammatory pain. J Neurosci. 1999;19:2181–6.
32. Constantin CE, Mair N, Sailer CA, Andratsch M, Xu ZZ, Blumer MJ, Scherbakov N, Davis JB, Bluethmann H, Ji RR, Kress M. Endogenous tumor necrosis factor alpha (TNFalpha) requires TNF receptor type 2 to generate heat hyperalgesia in a mouse cancer model. J Neurosci. 2008;28:5072–81.
33. Binshtok AM, Wang H, Zimmermann K, Amaya F, Vardeh D, Shi L, Brenner GJ, Ji RR, Bean BP, Woolf CJ, Samad TA. Nociceptors are interleukin-1beta sensors. J Neurosci. 2008;28:14062–73.
34. Ji RR, Samad TA, Jin SX, Schmoll R, Woolf CJ. p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. Neuron. 2002;36:57–68.
35. Obata K, Yamanaka H, Kobayashi K, Dai Y, Mizushima T, Katsura H, Fukuoka T, Tokunaga A, Noguchi K. Role of mitogen-activated protein kinase activation in injured and intact primary afferent neurons for mechanical and heat hypersensitivity after spinal nerve ligation. J Neurosci. 2004;24:10211–22.
36. Matsuda M, Oh-Hashi K, Yokota I, Sawa T, Amaya F. Acquired exchange protein directly activated by cyclic adenosine monophosphate activity induced by p38 mitogen-activated protein kinase in primary afferent neurons contributes to sustaining postincisional nociception. Anesthesiology. 2017;126:150–62.
37. Amaya F, Shimosato G, Nagano M, Ueda M, Hashimoto S, Tanaka Y, Suzuki H, Tanaka M. NGF and GDNF differentially regulate TRPV1 expression that contributes to development of inflammatory thermal hyperalgesia. Eur J Neurosci. 2004;20:2303–10.
38. Amaya F, Oh-hashi K, Naruse Y, Iijima N, Ueda M, Shimosato G, Tominaga M, Tanaka Y, Tanaka M. Local inflammation increases vanilloid receptor 1 expression within distinct subgroups of DRG neurons. Brain Res. 2003;963:190–6.
39. Obata K, Yamanaka H, Dai Y, Tachibana T, Fukuoka T, Tokunaga A, Yoshikawa H, Noguchi K. Differential activation of extracellular signal-regulated protein kinase in primary afferent neurons regulates brain-derived neurotrophic factor expression after peripheral inflammation and nerve injury. J Neurosci. 2003;23:4117–26.
40. Mizukoshi K, Sasaki M, Izumi Y, Miura M, Watanabe M, Amaya F. Activation of p38 mitogen-activated protein kinase in the dorsal root ganglion contributes to pain hypersensitivity after plantar incision. Neuroscience. 2013;234:77–87.
41. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. Trends Neurosci. 2009;32:611–8.
42. Mizushima T, Obata K, Yamanaka H, Dai Y, Fukuoka T, Tokunaga A, Mashimo T, Noguchi K. Activation of p38 MAPK in primary afferent neurons by noxious stimulation and its involvement in the development of thermal hyperalgesia. Pain. 2005;113:51–60.
43. Wen YR, Suter MR, Ji RR, Yeh GC, Wu YS, Wang KC, Kohno T, Sun WZ, Wang CC. Activation of p38 mitogen-activated protein kinase in spinal microglia contributes to incision-induced mechanical allodynia. Anesthesiology. 2009;110:155–65.
44. Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. Neurosci Bull. 2012;28:131–44.
45. Ren K, Dubner R. Interactions between the immune and nervous systems in pain. Nat Med. 2010;16:1267–76.
46. Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. Nat Neurosci. 2007;10:1361–8.
47. Liu XJ, Zhang Y, Liu T, Xu ZZ, Park CK, Berta T, Jiang D, Ji RR. Nociceptive neurons regulate innate and adaptive immunity and neuropathic pain through MyD88 adapter. Cell Res. 2014;24:1374–7.
48. Shibasaki M, Sasaki M, Miura M, Mizukoshi K, Ueno H, Hashimoto S, Tanaka Y, Amaya F. Induction of high mobility group box-1 in dorsal root ganglion contributes to pain hypersensitivity after peripheral nerve injury. Pain. 2010;149:514–21.
49. Ji RR, Xu ZZ, Strichartz G, Serhan CN. Emerging roles of resolvins in the resolution of inflammation and pain. Trends Neurosci. 2011;34:599–609.
50. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol. 2008;8:349–61.
51. Xu ZZ, Zhang L, Liu T, Park JY, Berta T, Yang R, Serhan CN, Ji RR. Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions. Nat Med. 2010;16:592–7.
52. Zhang L, Terrando N, Xu ZZ, Bang S, Jordt SE, Maixner W, Serhan CN, Ji RR. Distinct analgesic actions of DHA and DHA-derived specialized pro-resolving mediators on post-operative pain after bone fracture in mice. Front Pharmacol. 2018;9:412.
53. Mannion RJ, Costigan M, Decosterd I, Amaya F, Ma QP, Holstege JC, Ji RR, Acheson A, Lindsay RM, Wilkinson GA, Woolf CJ. Neurotrophins: peripherally and centrally acting modulators of tactile stimulus-induced inflammatory pain hypersensitivity. Proc Natl Acad Sci USA 1999;96:9385–90.
54. Kawasaki Y, Kohno T, Zhuang ZY, Brenner GJ, Wang H, Van Der MC, Befort K, Woolf CJ, Ji RR. Ionotropic and metabotropic receptors, protein kinase A, protein kinase C, and Src contribute to C-fiber-induced ERK activation and cAMP response element-binding protein phosphorylation in dorsal horn neurons, leading to central sensitization. J Neurosci. 2004;24:8310–21.
55. Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ. Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord. J Neurosci. 2002;22:6724–31.
56. Chen G, Xie RG, Gao YJ, Xu ZZ, Zhao LX, Bang S, Berta T, Park CK, Lay M, Chen W, Ji RR. beta-arrestin-2 regulates NMDA receptor function in spinal lamina II neurons and duration of persistent pain. Nat Commun. 2016;7:12531.
57. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. Nat Neurosci. 2012;15:1063–7.
58. Wei T, Li WW, Guo TZ, Zhao R, Wang L, Clark DJ, Oaklander AL, Schmelz M, Kingery WS. Post-junctional facilitation of Substance P signaling in a tibia fracture rat model of complex regional pain syndrome type I. Pain. 2009;144:278–86.
59. Chiu IM, Heesters BA, Ghasemlou N, von Hehn CA, Zhao F, Tran J, Wainger B, Strominger A, Muralidharan S, Horswill AR, Bubeck WJ, Hwang SW, Carroll MC, Woolf CJ. Bacteria activate sensory neurons that modulate pain and inflammation. Nature. 2013;501:52–7.
60. Chiu IM. Infection, pain, and itch. Neurosci Bull. 2018;34:109–19.
61. Xanthos DN, Sandkuhler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat Rev Neurosci. 2014;15:43–53.
62. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, Jonsson Fagerlund M, Charo IF, Akassoglou K, Maze

M. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol. 2011;70:986–95.
63. Shi Y, Gelman BB, Lisinicchia JG, Tang SJ. Chronic-pain-associated astrocytic reaction in the spinal cord dorsal horn of human immunodeficiency virus-infected patients. J Neurosci. 2012;32:10833–40.
64. Uceyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Schmid A, Casanova-Molla J, Reiners K, Sommer C. Small fibre pathology in patients with fibromyalgia syndrome. Brain. 2013;136:1857–67.
65. Ji RR, Berta T, Nedergaard M. Glia and pain: Is chronic pain a gliopathy? Pain. 2013;154 Suppl 1:S10–28.
66. Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. Nat Rev Neurosci. 2018;19:138–52.
67. Hanani M, Huang TY, Cherkas PS, Ledda M, Pannese E. Glial cell plasticity in sensory ganglia induced by nerve damage. Neuroscience. 2002;114:279–83.
68. Jasmin L, Vit JP, Bhargava A, Ohara PT. Can satellite glial cells be therapeutic targets for pain control? Neuron Glia Biol. 2010;6:63–71.
69. Berta T, Liu T, Liu YC, Xu ZZ, Ji RR. Acute morphine activates satellite glial cells and up-regulates IL-1beta in dorsal root ganglia in mice via matrix metalloprotease-9. Mol Pain. 2012;8:18.
70. Liu YC, Berta T, Liu T, Tan PH, Ji RR. Acute morphine induces matrix metalloproteinase-9 up-regulation in primary sensory neurons to mask opioid-induced analgesia in mice. Mol Pain. 2012;8:19.
71. Yamakita S, Horii Y, Takemura H, Matsuoka Y, Yamashita A, Yamaguchi Y, Matsuda M, Sawa T, Amaya F. Synergistic activation of ERK1/2 between A-fiber neurons and glial cells in the DRG contributes to pain hypersensitivity after tissue injury. Mol Pain. 2018;14:1744806918767508.
72. Colburn RW, Rickman AJ, DeLeo JA. The effect of site and type of nerve injury on spinal glial activation and neuropathic pain behavior. Exp Neurol. 1999;157:289–304.
73. Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, Inoue K. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature. 2003;424:778–83.
74. Kobayashi K, Takahashi E, Miyagawa Y, Yamanaka H, Noguchi K. Induction of the P2X7 receptor in spinal microglia in a neuropathic pain model. Neurosci Lett. 2011;504:57–61.
75. Kobayashi K, Yamanaka H, Fukuoka T, Dai Y, Obata K, Noguchi K. P2Y12 receptor upregulation in activated microglia is a gateway of p38 signaling and neuropathic pain. J Neurosci. 2008;28:2892–902.
76. Clark AK, Staniland AA, Malcangio M. Fractalkine/CX3CR1 signalling in chronic pain and inflammation. Curr Pharm Biotechnol. 2011;12:1707–14.
77. Jiang BC, Cao DL, Zhang X, Zhang ZJ, He LN, Li CH, Zhang WW, Wu XB, Berta T, Ji RR, Gao YJ. CXCL13 drives spinal astrocyte activation and neuropathic pain via CXCR5. J Clin Investig. 2016;126:745–61.
78. Tanga FY, Nutile-McMenemy N, DeLeo JA. The CNS role of Toll-like receptor 4 in innate neuroimmunity and painful neuropathy. Proc Natl Acad Sci USA. 2005;102:5856–861.
79. Kawasaki Y, Xu ZZ, Wang X, Park JY, Zhuang ZY, Tan PH, Gao YJ, Roy K, Corfas G, Lo EH, Ji RR. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. Nat Med. 2008;14:331–6.
80. Clark AK, Yip PK, Malcangio M. The liberation of fractalkine in the dorsal horn requires microglial cathepsin S. J Neurosci. 2009;29:6945–54.
81. Ji RR, Xu ZZ, Wang X, Lo EH. Matrix metalloprotease regulation of neuropathic pain. Trends Pharmacol Sci. 2009;30:336–40.
82. Jin SX, Zhuang ZY, Woolf CJ, Ji RR. p38 mitogen-activated protein kinase is activated after a spinal nerve ligation in spinal cord microglia and dorsal root ganglion neurons and contributes to the generation of neuropathic pain. J Neurosci. 2003;23:4017–22.
83. Tsuda M, Mizokoshi A, Shigemoto-Mogami Y, Koizumi S, Inoue K. Activation of p38 mitogen-activated protein kinase in spinal hyperactive microglia contributes to pain hypersensitivity following peripheral nerve injury. Glia. 2004;45:89–95.
84. Wen YR, Tan PH, Cheng JK, Liu YC, Ji RR. Microglia: a promising target for treating neuropathic and postoperative pain, and morphine tolerance. J Formos Med Assoc. 2011;110:487–94.
85. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci. 2008;28:5189–94.
86. Coull JA, Beggs S, Boudreau D, Boivin D, Tsuda M, Inoue K, Gravel C, Salter MW, De Koninck Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature. 2005;438:1017–21.
87. Suter MR, Berta T, Gao YJ, Decosterd I, Ji RR. Large A-fiber activity is required for microglial proliferation and p38 MAPK activation in the spinal cord: different effects of resiniferatoxin and bupivacaine on spinal microglial changes after spared nerve injury. Mol Pain. 2009;5:53.
88. Xu ZZ, Kim YH, Bang S, Zhang Y, Berta T, Wang F, Oh SB, Ji RR. Inhibition of mechanical allodynia in neuropathic pain by TLR5-mediated A-fiber blockade. Nat Med. 2015;21:1326–31.
89. Song P, Zhao ZQ. The involvement of glial cells in the development of morphine tolerance. Neurosci Res. 2001;39:281–6.
90. Ren K, Torres R. Role of interleukin-1beta during pain and inflammation. Brain Res Rev. 2009;60:57–64.
91. Chen G, Park CK, Xie RG, Berta T, Nedergaard M, Ji RR. Connexin-43 induces chemokine release from spinal cord astrocytes to maintain late-phase neuropathic pain in mice. Brain. 2014;137:2193–209.
92. Zhu X, Conklin D, Eisenach JC. Cyclooxygenase-1 in the spinal cord plays an important role in postoperative pain. Pain. 2003;104:15–23.
93. Zhu X, Eisenach JC. Cyclooxygenase-1 in the spinal cord is altered after peripheral nerve injury. Anesthesiology. 2003;99:1175–9.
94. Ying YL, Wei XH, Xu XB, She SZ, Zhou LJ, Lv J, Li D, Zheng B, Liu XG. Over-expression of P2X7 receptors in spinal glial cells contributes to the development of chronic postsurgical pain induced by skin/muscle incision and retraction (SMIR) in rats. Exp Neurol. 2014;261:836–43.
95. Christianson CA, Dumlao DS, Stokes JA, Dennis EA, Svensson CI, Corr M, Yaksh TL. Spinal TLR4 mediates the transition to a persistent mechanical hypersensitivity after the resolution of inflammation in serum-transferred arthritis. Pain. 2011;152:2881–91.
96. Wei T, Guo TZ, Li WW, Kingery WS, Clark JD. Acute versus chronic phase mechanisms in a rat model of CRPS. J Neuroinflammation. 2016;13:14.
97. Yang Q, Wu Z, Hadden JK, Odem MA, Zuo Y, Crook RJ, Frost JA, Walters ET. Persistent pain after spinal cord injury is maintained by primary afferent activity. J Neurosci. 2014;34:10765–9.
98. Dodick DW, Goadsby PJ, Silberstein SD, Lipton RB, Olesen J, Ashina M, Wilks K, Kudrow D, Kroll R, Kohrman B, Bargar R, Hirman J, Smith J. investigators ALDs: safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol. 2014;13:1100–7.

99. Loder E, Rizzoli P. Pharmacologic prevention of migraine: a narrative review of the state of the art in 2018. Headache. 2018. https://doi.org/10.1111/head.13375.
100. Pinho-Ribeiro FA, Baddal B, Haarsma R, O'Seaghdha M, Yang NJ, Blake KJ, Portley M, Verri WA, Dale JB, Wessels MR, Chiu IM. Blocking neuronal signaling to immune cells treats streptococcal invasive infection. Cell. 2018;173:1083–97.e22.
101. Loggia ML, Chonde DB, Akeju O, Arabasz G, Catana C, Edwards RR, Hill E, Hsu S, Izquierdo-Garcia D, Ji RR, Riley M, Wasan AD, Zurcher NR, Albrecht DS, Vangel MG, Rosen BR, Napadow V, Hooker JM. Evidence for brain glial activation in chronic pain patients. Brain. 2015;138:604–15.
102. Volkow ND, Collins FS. The role of science in addressing the opioid crisis. N Engl J Med. 2017;377:391–4.
103. Chen G, Park CK, Xie RG, Ji RR. Intrathecal bone marrow stromal cells inhibit neuropathic pain via TGF-beta secretion. J Clin Investig. 2015;125:3226–40.
104. Guo W, Wang H, Zou S, Gu M, Watanabe M, Wei F, Dubner R, Huang GT, Ren K. Bone marrow stromal cells produce long-term pain relief in rat models of persistent pain. Stem Cells. 2011;29:1294–303.
105. Huh Y, Ji RR, Chen G. Neuroinflammation, bone marrow stem cells, and chronic pain. Front Immunol. 2017;8:1014.
106. Barreto A, Braun TR. A method to induce interleukin-1 receptor antagonist protein from autologous whole blood. Cytokine. 2016;81:137–41.
107. Meijer H, Reinecke J, Becker C, Tholen G, Wehling P. The production of anti-inflammatory cytokines in whole blood by physico-chemical induction. Inflamm Res. 2003;52:404–7.
108. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res. 2017;12:16.
109. Sato KL, Johanek LM, Sanada LS, Sluka KA. Spinal cord stimulation reduces mechanical hyperalgesia and glial cell activation in animals with neuropathic pain. Anesth Analg. 2014;118:464–72.
110. Zhang RX, Li A, Liu B, Wang L, Ren K, Qiao JT, Berman BM, Lao L. Electroacupuncture attenuates bone cancer pain and inhibits spinal interleukin-1 beta expression in a rat model. Anesth Analg. 2007;105:1482–8.