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Role of immune cells in pain and emerging concepts of immunotherapy– A systemic review

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Abstract

Pain is the most common symptom of disease, which accompanies us from an early age. It is a protective mechanism to which the body responds to harmful stimulus. The definition of pain states that it is a subjective sensory and emotional experience.

Chronic pain is a major debilitating condition that is difficult to treat. Although chronic pain may appear to be a disorder of the nervous system, crucial roles for immune cells and their mediators have been identified as important contributors in various types of pain.

Chronic pain is caused by a lesion or disease of the somatosensory nervous system. It affects ~8% of the general population and negatively impacts a person's level of functioning and quality of life. Its resistance to available pain therapies makes pain a major unmet medical need. Immune cells have been shown to play a role for development, maintenance and recovery of chronic pain and therefore are attractive targets for novel pain therapies.

We discuss emerging roles of the immune system in resolving pain and how the immune system contributes to the transition from acute to chronic pain. We propose that targeting some of these immune processes may provide novel therapeutic opportunities for the treatment of chronic pain.

This review focuses on how the immune system regulates pain and discusses the emerging roles of immune cells in the initiation or maintenance of chronic pain. We highlight which immune cells infiltrate damaged nerves, the dorsal root ganglia, spinal cord and tissues around free nerve endings and discuss through which mechanisms they control pain.

Keywords: Chronic Pain, Immune Cells, Immune Response

Introduction

Pain is an unpleasant sensory and emotional feeling accompanying existing or impending tissue damage or referenced to such damage. Pain is the most common experience reported by patients, and patient anxiety is a form of warning signal. It is a sensual and perceptual phenomenon, which causes suffering and emotional state of risks connected with anxiety. Pain has many forms. It warns against damage to the body, which is important for avoiding injuries and consequently for survival [1].

Pain not caused by acute injuries can be unpleasant for the patient, or it can alter a person's life, reduce the quality of life, and also have an impact on the patient's family. The word "pain" for the patient means disease and suffering, for the

doctor it is a symptom, and for the physiologist it is a kind of feeling that has its own anatomical and physiological system which begins with the receptors and ends up in the brain cortex [2]. Feeling is a physical sensation that can be confirmed by electrophysiological methods, but in practice it is only a subjective sensation. It's intensity and quality come under various internal and external factors; therefore, the same stimulus can be experienced differently in different circumstances, somatic and psychiatric conditions [3].

The way of receiving pain is very individual and varies from time-to-time in the same individual. The intensity of pain is difficult to measure and an individual's perception of pain depends on the individual's emotional state, circumstances under which the pain was acquired, and whether it is perceived as a threatening signal. The perception of pain depends on such factors as arousal, attention, distraction and expectation [1].

Before we realize that something hurts, there are a number of physiological processes in our body. Painful stimuli have to be passed quickly – in (milli) seconds. Acute pain warns about impending or ensuing danger while chronic pain causes the afflicted part of the body, such as an immobilized and unused limb, increasing the chance for recovery [2].

A single, sharp stimulus to pain can disappear, and probably not leave a trail. Stimuli that are repeated, cause adaptive changes in the central nervous system and the activation of a number of systems, both supporting and inhibiting pain. In the spinal cord and the brain there occurs synthesis and the activation of various receptor systems, as well as synthesis of various compounds modifying the sense of pain[3].

It is known that an important role in this process is played the glial cells. It is a very complicated process that can lead to the preservation the pain, even after the disappearance of the pain stimulus[4].

Research from the last two decades has demonstrated that a robust neuro immune response and bidirectional signaling between the sensory and immune system contribute to development and maintenance of chronic pain. Indeed, increased levels of soluble pro-inflammatory mediators and recruitment of immune cells to the site of nerve injury, the dorsal root ganglion (DRG) and the spinal cord after PNS/CNS injury are well-characterized in rodent models of CNP [5,6]. In addition, immune cells also contribute to recovery of chronic pain, indicating that modulation of immunity has therapeutic potential to treat chronic pain.

Therefore, a detailed understanding of the contribution of immune responses to the development, maintenance and resolution of chronic pain may result in novel therapeutic approaches that are superior to current pain relieving therapies[7,8].

Physiology of pain

The cause of pain is irritation of the receptors, called nociceptors. Nociceptors are free nerve endings that respond to painful stimuli. Nociceptors are found in skin, organ of motion (periosteum, joint capsule, ligaments, muscles), cornea of the eye and dental pulp. Inside the body they are also abundant in the meninges, pleura, peritoneum and organ walls. Stimulated by biological, electrical, thermal, mechanical, and chemical stimuli they transmit information to the brain. When stimuli are transmitted to the spinal cord, then to the central areas of the brain, pain perception occurs. Impulses run to the dorsal horn of the spine, where they synapse with dorsal horn neurons in the substantia gelatinosa, and then enter the brain[7].

There are two types of fibres: Aδ and C, involved in pain transmission. The large one – Aδ fibres, produce sharp, well-defined pain, which is typically stimulated by a cut, an electrical shock, or a physical blow. They are myelinated and can allow an action potential to travel at a rate of about 20 meters/second towards the central nervous system[8,9].

Transmission through Aδ fibers is so fast that the body responds faster than the pain stimulus. This results in retraction of the affected body part before the person perceives the pain. This allows a quick response: "escape" or preparation for "fight". These fibres have practically no opioid receptors, while pain receptors located at the ends are always on standby. There are limited possibilities for pharmacological modification of these receptors.

In practice, it is easy to inhibit chronic, "slow" pain, using analgesic drugs and difficult to block "sharp", "fast" pain. After the so-called first pain, the smaller C fibres transmit dull burning or aching sensations, known as a "second pain." [10,11,12].

C fibres are very thin and susceptible to damage. They do not have the myelin sheath, therefore the conduction of painful stimuli is very slow – around 0.5 – 2 m/s. Numerous C fibres are combined in a "net"; therefore, the area covered by branching C-fibres is usually broad, and the patient is able to locate the pain only approximately. C fibres react to mechanical, thermal and chemical stimuli. They lead pain stimuli and also pruritic stimuli (which is a part of the fibres, especially sensitive to histamine). Patients describe pain conducted by C fibres as rapid, hitching, pulsing. At the ends of these nerve fibres there are different receptors, the most important of which are the opioid receptors[12].

Various cytokines produced by inflammatory cells are able to penetrate the damaged perineurium and activate the receptors. In this way, the opioid receptors are activated and after sensitization are able to react to endogenous and exogenous opioids. C-fibre nerve endings are also "sensitized" by prostaglandin and other mediators. Inhibition of prostaglandin synthesis a non-steroidal anti-inflammatory drug, and inhibition of inflammation by corticosteroids reduces the fibres nerve sensitivity and increase the pain threshold. This basic defence mechanism is based on the cooperation between the immune and nervous systems[13].

As a result, pain comes in two phases. The first phase is mediated by the fast-conducting Aδ fibers and the second part due to C fibres. Physiological pain has significant importance as a warning sign that ensure human safety[14]

Types of pain

Acute pain: Duration < 3 months, acts as a warning defensive (post-operative pain, traumatic, associated with medical procedures).

Chronic pain: Duration > 3 months, does not fulfil the role of warning and defensive, due to the nature and symptoms of the disease is considered in itself, and requires a multitherapeutic activities.

Survived pain: Most often occurs as a result of improper treatment of acute pain, persists despite the healed tissue, the damage to which resulted in acute pain.

Immune-derived mediators in pain initiation and maintenance

Several inflammatory mediators, such as bradykinin, histamine, adenosine triphosphate, neurotrophins and cytokines but also protons or damage-associated molecular patterns, activate sensory neurons to generate action potentials and/or enhance neuronal excitability and sensory transduction through neuronal receptors leading to pain and hyperalgesia[15,16].

The contribution of cytokines in initiating pain is supported by evidence that the development of inflammatory pain is attenuated by neutralizing cytokines or blocking cytokine receptors at the site of inflammation. Neutralization of TNFa with TNFa antibodies or soluble TNF receptors attenuates the development of pain in various experimental arthritis models[17]

The functional capacity of inflammatory mediators such as cytokines to produce pain is highly dependent on the expression and composition of their receptors in sensory neurons. Indeed, a wide range of cytokine receptors are expressed on sensory neurons, allowing cytokines to act directly on there [18,19].

During development of pain, expression of these receptors may be modulated, affecting the functional consequences of inflammatory mediators released. After peripheral nerve injury TNF receptors (TNFR1 and TNFR2) and their ligand, TNFa, are upregulated in sensory neurons. However, in several models of chronic pain, TNFR1 is the main pain promoting receptor, yet some reports indicate involvement of TNFR2 in pain induction[20,21]

Immune cells in pain initiation

Monocytes/macrophages are linked to the development of pain by the production of inflammatory mediators. In neuropathic (e.g., nerve injury-induced) and inflammatory pain models [e.g., arthritis, intraplantar complete Freund's adjuvant (CFA) injections] elevated numbers of monocytes/macrophages are observed in pain-relevant tissues such as the injured nerve, the inflamed skin at the time pain is developing.

Depletion of macrophages locally after CFA-induced paw inflammation attenuates the development of inflammatory pain, whilst depletion of macrophages at the site of inflammation during established persistent inflammatory pain does not affect pain [22].

Osteoclasts are derived from myeloid progenitors and play a role in the initiation of pain. In chronic inflammatory and degenerative diseases such as rheumatoid and osteo arthritis, osteoclasts are increased in number and display increased bone resorption activities[23].

These enhanced bone resorption activities cause local acidification, activating acid-sensing ion channels and transient receptor potential channel vanilloid subfamily member 1 in sensory neurons, leading to pain. Inhibitors of osteoclast activity reduce pain in models of osteo arthritis, inflammatory pain and cancer-induced bone pain [24,25].

Similarly, in humans inhibitors of osteoclast activity reduce pain in patients with bone disorders or rheumatoid arthritis. Although some studies have shown a role for myeloid cells or myeloid-derived osteoclasts in the initiation of pain, the majority of studies indicate roles for myeloid cells in pain maintenance.

Immune cells in pain maintenance

In rodent models of neuropathic pain, induced either surgically or by chemotherapy, monocytes/macrophages appear in the spinal cord at time points when pain is already established and these cells remain present for several weeks. In several chronic inflammatory pain models, including CFA-induced arthritis and experimental arthritis, macrophages are found in the DRG and spinal cord when pain is established[26].

The strongest evidence of the involvement of monocytes/ macrophages in the maintenance of chronic pain comes from monocyte/macrophage depletion studies. Depletion of peripheral macrophages by IV injections of clodronate liposomes partially reverses established paclitaxel-induced or nerve ligation-induced mechanical hyperalgesia and reduced TNFa [27].

Moreover, monocyte/macrophage depletion with clodronate liposomes delays the progression of diabetes-induced mechanical allodynia. Systemic depletion of monocytes/ macrophages after sciatic nerve ligation attenuates axonal damage and hyperalgesia, whereas depletion prior to L5 spinal nerve transection has no effect on the development of neuropathic pain, indicating that macrophages play a role in the maintenance of chronic pain[28,29].

The presence of macrophages at pain-relevant sites raises the question why these cells migrate to these tissues that are distant from the site of actual damage or inflammation. After peripheral inflammation sensory neurons produce chemokines chemokine (C-C motif) ligand 2 (CCL2) and chemokine (C-X3-C motif) ligand 1 (CX3CL1), which may drive the attraction of macrophages[30]. Similarly, after chemotherapy-induced nerve injury or after knee damage in an experimental osteoarthritis model, expression of CCL2 is increased in the DRG and spinal cord, and the increase in CCL2 production is associated with elevated numbers of macrophages in the DRG and spinal cord[30]. CX3CL1 is anchored to the plasma membrane, but is liberated after cleavage by proteases (e.g., cathepsin S) produced by activated microglia[31-34].

Immune cells in pain resolution

Depletion of monocytes prior to the induction of transient inflammatory pain with IL1b or carrageenan prevents the resolution of inflammatory pain, that normally last 12 days but now persists for >1 week. This prevention of the resolution of a transient inflammatory hyperalgesia is dependent on IL10 production by monocytes/macrophages.

Moreover, reduction of G protein-coupled receptor kinase 2, an ubiquitously expressed negative regulator of G protein-coupled receptors and other signaling molecules (e.g. p38) in monocytes/macrophages increases production of TNFa whilst reducing IL10 and prevents the resolution of transient inflammatory pain.

The existence of pain-resolving macrophages is further supported by evidence that perineural injection of IL4-skewed macrophages reduces neuropathic pain through the production of opioid peptides including Metenkephalin, dynorphin A and b-endorphin.

In conclusion, myeloid cells have distinct roles in the initiation, maintenance and resolution of pain. The functional plasticity of macrophages enables these cells to mediate both pro- and anti-nociceptive effects following injury or inflammation. As such, regulating macrophage phenotype by promoting polarization into anti-nociceptive or blocking polarization into pro-nociceptive phenotype might represent interesting avenues for potential new therapeutic strategies for chronic pain [35].

Neutrophils and mast cells pain initiation and resolution

After an inflammation/damage, neutrophils are one of the first cells recruited to the affected tissue and may act as potential initiators of pain. However, the majority of studies indicate that there is no substantial role for neutrophils in pain induction, since the development of inflammatory pain or incisional wound pain is not affected by neutrophil depletion[36]. Moreover, local recruitment of polymorphonuclear cells with CXCL1 and CXCL2/3 does not induce pain [37].

Given that mast cells are frequently found in close proximity to nerve endings, they are in a unique position to activate sensory neurons and induce pain. IgE-dependent activation of human mast cells induces itch. However, upon activation mast cells also rapidly release cytokines, NGF, proteases and histamine and bradykinin that induce pain[38,39].

In patients with chronic pain, such as inflammatory bowel syndrome, increased mast cell numbers are found in the inflamed tissues that correlated with the severity of pain symptoms. In rodents, degranulation of mast cells causes

immediate hyperalgesia in wild-type but not in mast-cell deficient mice. Although these results point to some role of mast cells and granulocytes in the initiation of pain, potential roles in maintaining pain are thus far unknown[39].

Pain resolution Neutrophils can release opioid peptides (b-endorphin, met-enkephalin and dynorphin-A) that have anti-nociceptive effects through m, d or k opioid receptors expressed by sensory neurons. An anti-nociceptive role of neutrophils is evoked by corticotrophin releasing factor (CRF) injections that induce opioid secretion by neutrophils. CRF attenuates CFA-induced inflammatory-hyperalgesia in rats in an opioid and granulocyte-dependent manner and intra-articular injections of CRF relieve postoperative pain in patients after arthroscopic knee surgery[40,41,42].

Immune cells	Role	Mediator
CD4+ Th1 cells	Promote pain development and maintenance	IL17A, leukocyte elastase
CD4+ Th2 cells	Promote pain recovery	IL-10, IL-4
CD8+ T cells (educated)	Promote pain recovery	IL-10
Tregs	Promote pain recovery	IL-10, IL-35, TGF-β, TNFR2
Inflammatory macrophages	Promote pain development and maintenance	CX3CL1, ROS
Anti-inflammatory macrophages	Alleviate pain	Endogenous opioids, TGF-β, IL-10

Table 1: overview of peripheral immune cell contribution to pain development and recovery

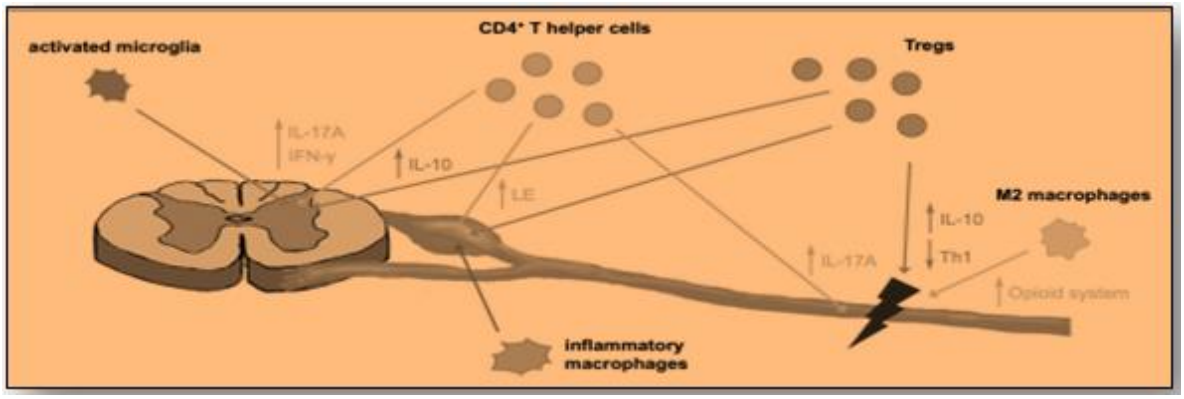

Figure 1: Contribution of different immune cells to pain development and recovery. CD4+ T helper cells were shown to infiltrate the spinal cord, DRG and injured nerve, where they contribute to pain responses through different mechanisms. Further, DRG invading macrophages were shown to be important mediators of pain. Like T effector cells, Tregs infiltrate the nerve, DRG, and spinal cord in neuropathic mice and contribute to immunomodulation and tissue regeneration through different mechanisms, including secretion of anti-inflammatory IL-10. M2 macrophages were shown to initiate analgesic responses in the nerve through upregulation of the endogenous opioid system and anti-inflammatory responses.

Immune response mechanism in dentine-pulp complex

The macroscopic and microscopic anatomy of the oral cavity is complex and unique in the human body. Soft-tissue structures are in close interaction with mineralized bone, but also dentine, cementum and enamel of our teeth. These are exposed to intense mechanical and chemical stress as well as to dense microbiologic colonization.

Teeth are susceptible to damage, most commonly to caries, where microorganisms from the oral cavity degrade the mineralized tissues of enamel and dentine and invade the soft connective tissue at the core, the dental pulp. However, the

pulp is well-equipped to sense and fend off bacteria and their products and mounts various and intricate defense mechanisms. The front rank is formed by a layer of odontoblasts, which line the pulp chamber towards the dentine.

These highly specialized cells not only form mineralized tissue but exert important functions as barrier cells. They recognize pathogens early in the process, secrete antibacterial compounds and neutralize bacterial toxins, initiate the immune response and alert other key players of the host defence.

As bacteria get closer to the pulp, additional cell types of the pulp, including fibroblasts, stem and immune cells, but also vascular and neuronal networks, contribute with a variety of distinct defence mechanisms, and inflammatory response mechanisms are critical for tissue homeostasis. Still, without therapeutic intervention, a deep carious lesion may lead to tissue necrosis, which allows bacteria to populate the root canal system and invade the periradicular bone via the apical foramen at the root tip.

The periodontal tissues and alveolar bone react to the insult with an inflammatory response, most commonly by the formation of an apical granuloma. Healing can occur after pathogen removal, which is achieved by disinfection and obturation of the pulp space by root canal treatment.

Immunotherapy

New designer immune-based biologic therapies are emerging from the increasing understanding of the molecular pathways associated with pain. Antibody therapies are most attractive for pharmaceutical development when a protein exerts a strong negative affect on a studied function such as pain excitation. Antibody therapies have high specificity with reduced off-target effects, which is not possible in many non-biologic therapies.

Anti ngf therapy

NGF is a potent neurotrophic factor during mammalian embryogenesis produced in limited amounts by innervation targets and required for the survival and development of nociceptors and sympathetic efferent. Immunotherapy trials have focused on targeting circulating NGF with NGF-sequestering agents to prevent NGF from binding to trkA, or to inhibit trkA function. Preclinical, phase I, II and III clinical trials have been completed for anti-NGF antibodies[44].

Anti-cgrp therapy

CGRP, part of the calcitonin family of peptide hormones, has two isoforms (α and β). The α isoform is a 37-amino-acid peptide that is released in the trigeminal ganglion after migraine triggers (eg, toxic, ischaemic, metabolic and inflammatory insults). Once released, it is a potent vasodilator in the meninges and is associated with release of nitrous oxide. CGRP can promote nociceptive signaling by a number of mechanisms, including (1) stimulation of satellite glial cells, (2) excitation of second-order neurons in the trigeminal nucleus (central sensitisation) and (3) excitation of primary afferent terminals (peripheral sensitisation)[4]

Conclusion

The contribution of immunity to development and maintenance of pain are well-established and a complex interaction of different immune cells contributes to pain development. Over the last years a growing body of literature on the protective and regenerative role of the immune system for pain has been published, including contributions of CD8+ T cells, Tregs and M2 macrophages.

Modulation of immune responses, e.g., by targeting inflammatory or anti-inflammatory mediators of peripheral immune cells, therefore is a promising therapeutic approach to alleviate neuropathic pain.

Concluding, a detailed understanding of immune-mediated tissue regeneration in pain may promote the development of novel immunotherapies for pain alleviation and ultimately may translate into novel non-opioid therapies.

References

1. Domżał T. Kliniczne podstawy badania i oceny bólu wprowadzenie do tematu. Pol Przegl Neurol. 2007; 3 (4), 211–215.

2. Thor P. Podstawy patofizjologii człowieka. In: Nowak Ł, Wordliczek J, Dobrogowski J. Mechanizmy bólu. 2nd ed. Kraków, 2007. p. 63–97 (in Polish).

3. Neural Plasticity and Disorders of the Nervous System. Cambridge University Press. Pain 2006.pp. 149–240

4. Żylicz Z, Krajnik M. Jak powstaje ból? Neurofizjologia bólu dla początkujących. Pol Med Paliat. 2003; 2(1): 49–56 (in Polish).

5. Sweitzer SM, Hickey WF, Rutkowski MD, Pahl JL, DeLeo JA. Focal peripheral nerve injury induces leukocyte trafficking into the central nervous system: potential relationship to neuropathic pain. Pain. (2002) 100:163– 70. doi: 10.1016/S0304-3959(02)00257-9

6. Moalem G, Xu K, Yu L. T lymphocytes play a role in neuropathic pain following peripheral nerve injury in rats. Neuroscience. (2004) 129:767– 77. doi: 10.1016/j.neuroscience.2004.08.035.

7. Austin PJ, Kim CF, Perera CJ, Moalem-Taylor G. Regulatory T cells attenuate neuropathic pain following peripheral nerve injury and experimental autoimmune neuritis. Pain. (2012) 153:1916–31. doi: 10.1016/j.pain.2012.06.005

8. Lees JG, Duffy SS, Perera CJ, Moalem-Taylor G. Depletion of Foxp3+ regulatory T cells increases severity of mechanical allodynia and significantly alters systemic cytokine levels following peripheral nerve injury. Cytokine. (2015) 71:207–14. doi: 10.1016/j.cyto.2014.10.028

9. Helms J. Barone C. Physiology and Treatment of Pain. Critical Care Nurse. 2008; 28 (6): 38–49.

10. Apkarian A, Bushnell M, Treede R, Zubieta J. Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain. 2005; 9: 463–484.

11. Konturek J. Fizjologia człowieka. In: Sadowski B. Bol. 1 st ed. Wroclaw, 2007. p. 912–921 (in Polish).

12. Schmidt R, Schmelz M, Ring Kamp M, Handwerker HO, Tore Björk HE. Innervation territories of mechanically activated C nociceptor units in human skin. J. Neurophysiol. 1997; 78: 2641–2648.

13. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Tore Björk HE. Specific C-receptors for itch in human skin. J. Neurosci. 1997; 17: 8003–8008.

14. Stein C. The control of pain in peripheral tissue by opioids. N. Engl. J. Med. 1995; 332: 1685–1690.

15. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007; 45:2737.

16. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009; 139:26784.

17. Boettger MK, Hensellek S, Richter F et al. Antinociceptive effects of tumor necrosis factor alpha neutralization in a rat model of antigen-induced arthritis: evidence of a neuronal target. Arthritis Rheum 2008; 58:236878.

18. Usoskin D, Furlan A, Islam S et al. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. Nat Neurosci 2015; 18:14553.

19. Miller RJ, Jung H, Bhangoo SK, White FA. Cytokine and chemokine regulation of sensory neuron function. Handb Exp Pharmacol 2009;41749.

20. George A, Buehl A, Sommer C. Tumor necrosis factor receptor 1 and 2 proteins are differentially regulated during Wallerian degeneration of mouse sciatic nerve. Exp Neurol 2005; 192:1636.

21. Leung L, Cahill CM. TNF-alpha and neuropathic pain—a review. J Neuroinflammation 2010; 7:27.

22. Nagae M, Hiraga T, Yoneda T. Acidic microenvironment created by osteoclasts causes bone pain associated with tumor colonization. J Bone Miner Metab 2007; 25:99104.

23. Reeh PW, Kress M. Molecular physiology of proton transduction in nociceptors. Curr Opin Pharmacol 2001; 1:4551.

24. Nagae M, Hiraga T, Wakabayashi H et al. Osteoclasts play a part in pain due to the inflammation adjacent to bone. Bone 2006; 39:110715.

25. Strassle BW, Mark L, Leventhal L et al. Inhibition of osteoclasts prevents cartilage loss and pain in a rat model of degenerative joint disease. Osteoarthritis Cartilage 2010; 18:131928.

26. Barclay J, Clark AK, Ganju P et al. Role of the cysteine protease cathepsin S in neuropathic hyperalgesia. Pain 2007; 130:22534.

27. 112 Zhang H, Li Y, de Carvalho-Barbosa M et al. Dorsal root ganglion infiltration by macrophages contributes to paclitaxel chemotherapy-induced peripheral neuropathy. J Pain 2016; 17:77586.

28. Mert T, Gunay I, Ocal I et al. Macrophage depletion delays progression of neuropathic pain in diabetic animals. Naunyn Schmiedebergs Arch Pharmacol 2009; 379:44552.

29. Liu T, van Rooijen N, Tracey DJ. Depletion of macrophages reduces axonal degeneration and hyperalgesia following nerve injury. Pain 2000; 86:2532.

30. Rutkowski MD, Pahl JL, Sweitzer S, van Rooijen N, DeLeo JA. Limited role of macrophages in generation of nerve injury-induced mechanical allodynia. Physiol Behav 2000; 71:22535.

31. Jeon SM, Lee KM, Park ES, Jeon YH, Cho HJ. Monocyte chemoattractant protein-1 immunoreactivity in sensory ganglia and hind paw after adjuvant injection. Neuroreport 2008; 19:1836.

32. Souza GR, Talbot J, Lotufo CM et al. Fractalkine mediates inflammatory pain through activation of satellite glial cells. Proc Natl Acad Sci U S A 2013; 110:111938.

33. Clark AK, Yip PK, Malc Angio M. The liberation of fractalkine in the dorsal horn requires microglial cathepsin S. J Neurosci 2009; 29:694554.

34. Verge GM, Milligan ED, Maier SF et al. Fractalkine (CX3CL1) and fractalkine receptor (CX3CR1) distribution in spinal cord and dorsal root ganglia under basal and neuropathic pain conditions. Eur J Neurosci 2004; 20:115060

35. Pannell M, Labuz D, Celik MO et al. Adoptive transfer of M2 macrophages reduces neuropathic pain via opioid peptides. J Neuroinflammation 2016; 13:262.

36. Rittner HL, Mousa SA, Labuz D et al. Selective local PMN recruitment by CXCL1 or CXCL2/3 injection does not cause inflammatory pain. J Leukoc Biol 2006; 79:102232.

37. Forsythe P, Bienenstock J. The mast cell-nerve functional unit: a key component of physiologic and https://academic.oup.com/rheumatology 439 Immune cells in pain Downloaded from https: //academic .oup.com /rheumatology /article /57/3/429/4080841 by guest on 15 October 2021 pathophysiologic responses. Chem Immunol Allergy 2012; 98:19622

38. Barbara G, Stanghellini V, De Giorgio R, Corinaldesi R. Functional gastrointestinal disorders and mast cells: implications for therapy. Neurogastroenterol Motil 2006; 18:617.

39. Nigrovic PA, Lee DM. Mast cells in inflammatory arthritis. Arthritis Res Ther 2005; 7:111.

40. Chatterjea D, Martinov T. Mast cells: versatile gatekeepers of pain. Mol Immunol 2015; 63:3844.

41. Chatterjea D, Wetzel A, Mack M et al. Mast cell degranulation mediates compound 48/80-induced hyperalgesia in mice. Biochem Biophys Res Commune 2012; 425:23743.

42. Stein C. Opioids, sensory systems and chronic pain. Eur J Pharmacol 2013; 716:17987.

43. Brack A, Rittner HL, Machel ska H et al. Control of inflammatory pain by chemokine-mediated recruitment of opioid-containing polymorphonuclear cells. Pain 2004; 112:22938.

44. Chang DS, Hsu E, Hottinger DG, et al. Anti-nerve growth factor in pain management: current evidence. J Pain Res 2016; 9:373–83