OPEN

PAIN REPORTS®

Sensory neuron–associated macrophages as novel modulators of neuropathic pain

Conceição Elidianne Aníbal Silva[a,b], Rafaela Mano Guimarães[a,b], Thiago Mattar Cunha[a,c,*]

Abstract

The peripheral nervous system comprises an infinity of neural networks that act in the communication between the central nervous system and the most diverse tissues of the body. Along with the extension of the primary sensory neurons (axons and cell bodies), a population of resident macrophages has been described. These newly called sensory neuron–associated macrophages (sNAMs) seem to play an essential role in physiological and pathophysiological processes, including infection, autoimmunity, nerve degeneration/regeneration, and chronic neuropathic pain. After different types of peripheral nerve injury, there is an increase in the number and activation of sNAMs in the sciatic nerve and sensory ganglia. The activation of sNAMs and their participation in neuropathic pain development depends on the stimulation of pattern recognition receptors such as Toll-like receptors and Nod-like receptors, chemokines/cytokines, and microRNAs. On activation, sNAMs trigger the production of critical inflammatory mediators such as proinflammatory cytokines (eg, TNF and IL-1β) and reactive oxygen species that can act in the amplification of primary sensory neurons sensitization. On the other hand, there is evidence that sNAMs can produce antinociceptive mediators (eg, IL-10) that counteract neuropathic pain development. This review will present the cellular and molecular mechanisms behind the participation of sNAMs in peripheral nerve injury–induced neuropathic pain development. Understanding how sNAMs are activated and responding to nerve injury can help set novel targets for the control of neuropathic pain.

Keywords: Neuropathic pain, Primary sensory neurons, Macrophages, Cytokines, Chemokines

Key Points:

1. Sensory neuron–associated macrophages (sNAMs) are involved in the pathophysiology of neuropathic pain through the production of proinflammatory and pronociceptive mediators.
2. Sensory neuron–associated macrophages are activated in the sensory ganglia after peripheral nerve injury mainly by PRRs and chemokines.
3. Sensory neuron–associated macrophages also produce anti-inflammatory mediators that counteract neuropathic pain development such as IL-10.
4. Understanding the interactions between injured sensory neurons and sNAMs can provide novel targets for neuropathic pain control.

1. Introduction

According to the current IASP definition, pain can be defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[202] In other words, pain is a personal complex experience that includes the conscious perception of a stimulus capable of generating tissue damage and may further depend on cognitive and emotional components.[37,91,216,224] Whereas acute pain has a protective function to avoid potential damage, chronic pain can be maladaptive and pathological, and it represents one of the most prevalent and disabling health conditions in modern society.[136,202] Neuropathic pain is a type of chronic pain characterized by injury or disease that directly affects the somatosensory nervous system, including peripheral fibers and central neurons.[202] Epidemiological studies estimate that this pathology affects an average of 7% to 10% of the general population, being one of the most prevalent health problem.[38,110,190] The mechanisms involved in the development and maintenance of neuropathic pain were initially characterized as a neuronal dysfunction. Indeed, after nerve injury, a series of

modifications occur across the pain pathway that includes alterations in ion channel expression and function, upregulation of neurotransmitters, and their receptors, which leads to a state of neuronal hyperexcitability.[13,43,46,50,54,61,77,119,145,176,205]

Currently, there is a growing body of evidence indicating that the cause of neuropathic pain is not restricted to changes in neuronal activity but may involve a network of interaction among neurons, glial, and immune cells.[37,48,78,86–88,240] These cells may interact with neuronal cell bodies and their fibers distributed throughout the peripheral and central nervous system (CNS) in both pathological or homeostatic conditions. In the case of neuropathic pain, when nerve integrity is affected, immune/glial cells, which may be resident or recruited to the injured tissue, and distally to the sensory ganglia and spinal cord, are activated and release inflammatory mediators that strongly modify neuronal function, culminating in alterations of painful perception.[165,223,236] Among the immune/glial cells, macrophages emerge as one of the most important cell subpopulations involved in neuroimmune interactions associated with neuropathic pain.[57,161,225] This review discusses the current evidence regarding the cellular and molecular interactions between primary sensory neurons and resident macrophages associated with these peripheral neurons, known as sensory neuron–associated macrophages (sNAMs), that might play a crucial role in the development of neuropathic pain. The role of infiltrating monocytes in the site of nerve injury is also discussed. Finally, we pointed out additional mechanisms by which peripheral macrophages may also counteract neuropathic pain development.

2. Neuron associated–macrophages: their origins and fate

Tissue-resident macrophage populations are present in a variety of organs across the body.[166,228,240] Although some characteristics and functions are shared among different macrophage populations, such as homeostasis maintenance and tissue protection, these cells exhibit high functional plasticity and thus have several specialized functions in each different niche/tissue.[58–133,133–136,138–166]

Historically, distinct subpopulations of macrophages have been defined according to the anatomical location and surface markers; however, this definition has been recently expanded to subset-specific gene expression signatures[181] and ontogenies of these cell populations.[56] It was known that monocytes newly released from bone marrow colonize various tissues, and once mature, they may become resident macrophages with specific features. It is currently accepted that most cells in the hematopoietic compartment are regularly renewed from adult hematopoietic stem cells (HSCs); however, recent findings demonstrate that resident macrophages can self-maintain independently of HSCs because they may have an embryonic origin. In this scenario, it is known that, at least in mice, tissue macrophages are derived from 3 different developmental sources.[60,70,166,210] Macrophages firstly appear in the yolk sac (YS) during initial fetal development without monocytic intermediates and then colonize various embryonic tissues.[179] In the embryonic period 8.5 (E8.5), macrophage precursors from the YS and HSCs migrate to the fetal liver and give rise to the first monocyte cells in E12.5.[79,142] After birth, HSC in the bone marrow produces Ly6C+ monocytes, which can migrate to different tissues and differentiate into macrophages.[76,220]

Based on this, some groups have performed extensive characterizations of resident macrophages in the most diverse tissues, based not only on the anatomical location and profile of phenotypic markers but also on the transcriptional and ontogeny

profile. In this sense, Gomez Perdiguero et al.[63] proposed that macrophages of the liver, lung, and epidermis are originated from YS-derived erythro-myeloid progenitors. The CNS also has resident macrophages with specific characteristics, including self-sustainability and proliferation. Besides microglia, meningeal, perivascular, and choroid plexus macrophages are considered CNS interface cells that appear to be derived from the YS, demonstrating that different populations of CNS macrophages share similar ontogeny.[59,62]

In addition to the macrophages residing in the CNS, peripheral nerves also contain resident macrophages.[113] These macrophages are distributed in the large peripheral nervous system interaction network and comprise one of the most important populations of myeloid cells associated with peripheral nervous tissue. For instance, in the rat, sciatic nerve macrophages constitute 1% to 4% of the total cell population.[162] Conceptually, the term NAMs defines the subset of resident tissue macrophages that are closely associated with peripheral nerves in the most diverse tissues[113] and can be characterized by the type of tissue and nerve in which they reside, origin, and self-renewal characteristic. The identification of macrophages in peripheral nerves occurred many years ago. In a pioneering study by Arvidson[10] when examining the sciatic nerve of animals after the systemic injection of horseradish peroxidase, an enzymatic tracer that is widely distributed in most tissues, he observed through electron microscopy, cells with similar ultrastructural characteristics macrophages and located close to the epineurial and endoneurial. Later, Gehrmann et al.[55] were able to demonstrate the presence of macrophages in the sciatic nerve and the dorsal root ganglions (DRGs), where the cellular bodies of sensory neurons are located. They confirmed the presence of macrophages in the DRGs by evaluating the expression of classic cell markers, such as CR3 and MHC-II, by immunohistochemistry reaction. Despite these data, only recently, sNAMs broad characterization was performed. Importantly, it was found that sNAMs from different neuronal compartments (sciatic nerve, DRGs, and cutaneous intercostal fascial nerves) are mostly self-maintained in adult mice.[112,219] Contrary, ontology analysis of sNAMs of the sciatic nerves revealed they are predominantly from late embryonic precursors that are slowly replaced by bone marrow–derived monocytes.[231] Therefore, further studies are important to finally define the origin of distinct sNAMs from different neural niches. Transcriptome analysis also revealed that sNAMs share some characteristics with activated microglia. However, sNAMs-specific genes were also identified, including genes related to angiogenesis, collagen fibril organization, and peripheral nerve structural organization and axon guidance.[219] This specific transcriptional profile of sNAMs is in line with their possible role in axon sprouting after peripheral nerve injury.[112] Besides that, the participation of sNAMs in the pathophysiology of neuropathic pain has been extensively studied, and these studies will be discussed below.

3. The sensory neuron–associated macrophages in the development of neuropathic pain

Neuropathic pain, the focus of this review, can occur because of several stressors, such as viral infections, diabetic neuropathy, mechanical trauma, neurotoxic chemicals, spinal cord injury, stroke, and multiple sclerosis.[38,77,110,190,221] Models of peripheral nerve injury are widely used to mimic neuropathic pain and most of the common clinical characteristics of this pathology. The development of neuropathic pain models has been fundamental for characterizing pathophysiological mechanisms and has shed

new light on the preclinical evaluation of potential therapeutic interventions.[119]

The injury of primary afferent neurons conducts these cells to a hyperexcitability state. Thus, the action potentials generated at their endings are easily carried forward to the second-order neurons in the dorsal horn of the spinal cord and later to supraspinal brain regions, where the painful sensation is processed and interpreted.[18,43] It is currently well accepted that the interactions of immune and glial cells within the peripheral nervous system and CNS regulate neuronal excitability and sensitize the pain pathway.[145,155] When nerve integrity is disrupted, neuroimmune interactions occur early in the local of injury and register the initial trigger for neuropathic pain development. Resident cells, including Schwann cells and sNAMs, are responsible for the production of earlier inflammatory mediators that mediate the recruitment of immune cells to the injured nerve.[9,47] After a peripheral nerve trauma, initial recruitment of neutrophils occurs, followed by the infiltration of inflammatory CCR2+ monocytes, which might be important to amplify the immune response.[1,93] Studies show that systemic treatment with chemotherapy drugs, which are well known as neurotoxic, promoted an increase in the number of CX3CR1+ and CCR2+ macrophages/monocytes in the peripheral nerves.[146] Several studies suggested that these locally activated macrophages are directly associated with a significant increase in the levels of inflammatory mediators, which sensitize primary afferent neurons and contribute to the development of neuropathic pain.[51,57,66,130,148,236] For instance, Cx3cr1-deficient or Ccr2-deficient showed delayed development of mechanical hypersensitivity caused by the treatment with chemotherapy drug vincristine.[146] Although resident and infiltrated macrophages/monocytes at the site of nerve injury are considered essential for the development of neuropathic pain, most of the studies that claimed this possibility lack specific tools targeting only these cells to confirm this hypothesis. Given these methodological limitations, many efforts have been made to develop specific tools to precisely manipulate peripheral (resident and infiltrating) vs central (eg, microglia)[44,45].

One of those promising examples is a recently described mouse strain in which the suicidal gene Fas is under the control of the colony-stimulating factor 1 receptor (CSF1R) promoter, called macrophage-induced fas-apoptosis (MAFIA).[24] In these mice, Fas ligand administration drives the death of CSF1R+ cells. Unlike CSFR1 selective antagonists, this drug fails to cross the blood–brain barrier, ensuring higher peripheral macrophage specificity. By taking advantage of MAFIA mice, Shepherd et al.[183] showed alleviation of mechanical pain hypersensitivity caused by peripheral nerve injury. The authors implicated the reduction in infiltrated monocytes as responsible for the MAFIA mouse pain phenotype.[183] On the other hand, more recently, it was shown that specific depletion of macrophages/monocytes at the site of nerve injury did not affect the development of neuropathic pain, excluding any participation of macrophages/monocytes in the local of nerve injury for the development of neuropathic pain.[235] Thus, although the systemic depletion of peripheral macrophages/monocytes reduces neuropathic pain development,[31,161,193] it is likely that these cells could be acting in tissues different from the local nerve injury.

Besides the peripheral nerves resident sNAMs, as we mentioned above, there are also resident sNAMs in the sensory ganglia (DRGs and TGs). The injury of peripheral nerves promotes several changes at the level of sensory ganglia, including a neuroinflammatory process characterized by activation/proliferation of glial cells (eg, satellite glial cells [SGCs]), and

sNAMs. Early studies using different sciatic nerve trauma models described an increase in the number of macrophages/monocytes around the cell body of sensory neurons in the sensory ganglia in a time-dependent manner.[108,117,235,238] Generally, the number of macrophages peaks form 5 to 10 days after sciatic nerve injury, retracting afterward.[117,128,200] In chemotherapy-induced peripheral neuropathy, an accumulation of macrophages in the DRGs was also observed by some groups, whereas others did not observe any change.[89,104,133,139,141,238] Although the reasons for this discrepancy are not immediately apparent, it could be related to differences in the doses of the chemotherapy drug used, schedules of treatment, and evaluated time points. There is another debate regarding whether the accumulation of macrophages in the sensory ganglia after peripheral nerve injury is due to the infiltration of blood monocytes or the local proliferation of sNAMs. Thus, further studies will also be necessary to clarify this point.

To dissect the participation of sNAMs in the sensory ganglia for the development of neuropathic pain, some strategies were applied. The intrathecal administration of minocycline reduced the number of sNAMs in the DRG after peripheral nerve injury, which was accompanied by the downregulation of inflammatory mediators reflecting on the reduction of mechanical pain hypersensitivity.[117] A combination of genetic and pharmacological tools for conditional depletion of peripheral sNAMs/monocytes and microglia also prevented the development of pain hypersensitivity in a mouse model of spinal nerve transection.[165] Targeting peripheral macrophage and microglia with CSFR1 inhibitor, a receptor involved in survival, proliferation, and differentiation of macrophages in different tissues, also reduced neuropathic pain caused by peripheral nerve injury.[121] In addition, the clodronate-induced killing of sensory ganglia macrophages reduced neuropathic pain development caused by peripheral nerve injury (trauma) and chemotherapy (paclitaxel).[36,238] Noteworthy, none of these treatments are selective for sNAMs in the sensory ganglia and also target infiltrating monocytes and/or microglia. Based on that, the same study that ruled out the contribution of nerve injury–infiltrating macrophages for the development of neuropathic pain provided evidence that sNAMs in the sensory ganglia play a critical role in this condition.[235] However, we could not discard those peripheral monocytes could be acting in additional sites than the local of nerve injury. For instance, we recently found that after peripheral nerve injury, CCR2+ monocytes become adhered to the endothelial cells of the spinal cord microcirculation, and these cells could also have a role in central mechanisms of neuropathic pain[71]. Finally, it is important to mention that the discovery of specific cellular markers for sNAMs of the sensory ganglia that could differentiate them from other resident macrophages and monocytes would be essential to develop specific strategies to target only these cells and dissect their real contribution to neuropathic pain development.

4. Mechanisms of sensory neuron–associated macrophages activation and accumulation after nerve injury

As we mentioned above, after peripheral nerve injury, the activation/accumulation of sNAMs in the sensory ganglia (DRGs) seems to play an essential role in the development of neuropathic pain. Although it is not totally clear how the peripheral nerve injury leads to the distal activation/accumulation of sNAMs in the sensory ganglia, some possible mechanisms have been proposed.

4.1. sNAMs and innate immunity receptors

Like classical immune cells, macrophages can express different innate immunity receptors, such as Toll-like receptors (TLRs) and nucleotide-binding cytoplasmic oligomerization (NLRs) receptors.[26,41,108,160,195–197,233] The large family of TLRs plays a critical role in immune responses by the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs),[2] such as heat shock proteins, necrotic cells, and extracellular matrix components.[2,19,21,111,123,133,134,163,192,197,239] Continuous activation or dysregulation of TLRs signaling may contribute to chronic disease states and have been involved in the pathogenesis of neuroinflammation, including in neuropathic pain development.[28,152,222] In this sense, several studies have indicated that the activation/proliferation of microglia in the spinal cord, after peripheral nerve injury, that accounts for neuropathic pain development might depend on TLRs stimulation.[132] For instance, Shi et al. demonstrated that spinal cord microglia activation after peripheral nerve injury depends on an unidentified endogenous ligand of TLR2 derived from damaged peripheral nerves.[184] More recently, it was found that after peripheral nerve injury, GT1b ganglioside is axonally transported from the cell body of sensory neurons into the spinal cord and mediates neuropathic pain development through the activation of TLR2.[126]

Regarding the role of TLRs in sNAMs activation, TLR2 null mice also showed a reduction in the activation/accumulation of sNAMs in the sensory ganglia.[108] This effect seems to be related to a decrease in the production of CCL2 in the sensory ganglia, which is a crucial chemokine in macrophages activation/infiltration.[108] Although a direct TLR2 activation of sNAMs in the sensory ganglia may likely occur after peripheral nerve injury, we could not discard an indirect activation because TLR2 seems to be also expressed on different cells (eg, SGCs) of the sensory ganglia.[108] Furthermore, there is evidence that TLR2 deficiency also reduced macrophages' infiltration at the nerve injury site,[184] which could also indirectly affect neuroinflammation in the DRGs.

Another pattern recognition receptor (PRR) which has been described as important for neuropathic pain development is TLR4.[132] Earlier studies have shown that TLR4 deficient mice are protected from peripheral nerve injury–induced neuropathic pain.[17,206] This effect was attributed to reducing microglia activation in the spinal cord.[26,197] However, no one has evaluated the impact of TLR4 deficiency in sNAMs activation in the sensory ganglia in models of traumatic peripheral nerve injury. There is also evidence that TLR4 mediates chemotherapy-induced peripheral neuropathic pain (eg, paclitaxel and oxaliplatin).[122,148,230] In paclitaxel-induced neuropathic pain, the blockage of TLR4 reduced the accumulation of macrophages in sensory ganglia.[237]

Nevertheless, this was assumed as a direct effect of paclitaxel on the activation of TLR4 expressed in sensory neurons, which in turn increased the production of the macrophages chemotactic factor, CCL2.[237] Activation of SGCs by paclitaxel in a TLR4-dependent manner and the consequent production of proinflammatory cytokines have also been suggested as a possible mechanism involved in neuropathic pain development.[226] Although the contribution of TLR4 in sensory ganglia sNAMs for paclitaxel-induced neuropathic pain has been not investigated, it could also be an alternative. In this context, it was recently found that DRGs sNAMs-expressing TLR4 mediates the development of oxaliplatin-induced neuropathic pain.[180] A recent study also revealed a role for TLR9 signaling in the pathophysiology of paclitaxel-induced neuropathic pain.[137] In fact, Luo and

collaborators demonstrated that paclitaxel-induced neuropathic pain was impaired in TLR9 KO mice and by the intrathecal administration of a TLR9 selective antagonist. Pain hypersensitivity was also mimicked by intraplantar and intrathecal injection of a TLR9 agonist (ODN 1826). Notably, TLR9 was found in DRG sNAMs and seemed to involve the induction of proinflammatory factors, such as cytokines.

Together with TLRs, cytoplasmic nucleotide-binding oligomerization domain-like receptors (NLRs) are the most important receptors responsible for the recognition of PAMPs or DAMPs.[19,37] An important example of a receptor in this family is the nucleotide-binding oligomerization domain 2 (NOD2). Some studies indicate that microglial cells express NOD2,[29,31,194] suggesting a possible role of this receptor as an innate immune sensor in the CNS. It is well established that NOD2 and TLRs act in macrophages' activation, leading to positive pressure in the proinflammatory pathways.[72] We recently demonstrated that after peripheral nerve injury, the NOD2 expression is upregulated in sNAMs of the sensory ganglia.[175] Using genetic inhibition of NOD2, we showed that NOD2 signaling is involved in sensory ganglia sNAMs activation/accumulation and mediates neuropathic pain development. On stimulation, NOD2 directly recruits the receptor-interacting serine/threonine-protein kinase 2, which is important for nuclear transcription factor kappa B activation and the transcription of proinflammatory genes.[75,175] In this context, pharmacological inhibition of receptor-interacting serine/threonine-protein kinase 2 activity with a selective inhibitor (WEHI-345) also reduced the development of neuropathic pain.[175] Altogether these studies provide consistent evidence that the manipulation of PRRs (eg, TLRs and NLRs) or their downstream signaling in sNAMs of the sensory ganglia could be explored as targets to prevent the development of peripheral neuropathic pain.

The involvement of PRRs in the activation of sensory ganglia sNAMs that account for neuropathic pain development raised the question of how these cells recognize or respond to peripheral nerve injury, which is assumed to be a sterile condition. Previous studies have suggested that damaged peripheral sensory neurons release DAMPs, such as fibronectin, high mobility group box-1, and heat shock proteins, which in turn can activate some TLRs.[201,207,208] These DAMPs have been shown to induce further activation of numerous cell types, including glial cells and innate immune cells, which have a well-established role in the process of neuropathic pain.[65,133,178] We recently demonstrated that neutrophil-derived S100a9, an endogenous stimulator of TLR4 signaling, plays an essential role in a model of herpetic neuralgia in a mechanism dependent on activation of TLR4 in sNAMs.[188] Another possibility in the activation of sNAMs PRRs after nerve injury would be by PAMPs derived from microbiota. In fact, a broader role for the microbiota as a significant modulator of systemic immunity has been proposed.[99,156,173] Microbial products derived from the microbiota can be excreted or translocated across the gut mucosa into the systemic circulation during infection or inflammation.[35,115] These processes are involved in the development of several diseases, such as autoimmune diseases, Parkinson's disease, spinal cord injury, and neuropsychiatric disorders.[103,120,140] For instance, bacterial microbiota–derived peptidoglycan and methylene diphosphonate are presented in rheumatoid arthritis patients' synovial tissue, contributing to the pathogenesis through NOD2 signaling activation.[90,143] In addition, peptidoglycan-containing immune cells were detected in the CNS of multiple sclerosis patients or animals but not in healthy controls.[214,215] Our group has shown that germ-free mice are resistant to inflammatory pain[4]. We also

found that peripheral nerve injury can promote a systemic increase of an undetermined stimulant of NOD2 signaling.[188] Thus, it is possible that after peripheral nerve injury gut microbiota–derived PAMPs (TLRs and NOD2 ligand; eg, lipopolysaccharides, peptidoglycan, and/or methylene diphosphonate) may translocate from the luminal side of the gut into the blood to distal sites (eg, sensory ganglia), activates PRRs signaling in sNAMs, and consequently contribute to the development of neuropathic pain. This hypothesis is supported by our unpublished data in which we found that there is impairment in the intestinal barrier permeability after spared nerve injury in mice. Furthermore, in a model of chemotherapy-induced neuropathic pain, there is an increase in the concentration of microbiota-derived lipopolysaccharides in the DRGs, which triggers a TLR4 dependent activation of sNAMs.[180] Nevertheless, further studies would be important to identify the exact origin of PAMPs or DAMPs that mediate sNAMs activation in the sensory ganglia and contribute to neuropathic pain development.

4.2. Additional mechanisms of sensory neuron–associated macrophages activation/accumulation after peripheral nerve injury

Besides the role of PRRs in the activation/accumulation of sNAMs in the sensory ganglia after peripheral nerve injury, emerging studies were designed to find additional mechanisms explaining how distal damage to primary sensory neurons could activate sensory neurons sNAMs and consequently to the development and maintenance of neuropathic pain. Among these possible mechanisms, the most characterized are those dependent on chemokines (CCL2/CCR2 and CX3CL1/CX3CR1 pathways), cytokines (CSF1/CSFR1 axis), and microRNAs.

4.3. Chemokines/cytokines trigger sensory neuron–associated macrophages activation

Among the central communication systems of sNAMs and their microenvironments are the chemokine/chemokine receptors interaction. Chemokines are a vast group of peptides that act primarily to attract leukocytes to a given environment after infection or tissue damage.[169–171] These molecules act on receptors coupled to G proteins found in different populations of circulating and resident cells. Two important chemokine axis seem to regulate sNAMs activities: (1) the CX3CL1, also known as Fractalkine, and its receptor CX3CR1[32–34]; (2) CCL2, also known as MCP-1, and its receptor CCR2 CX3CR1 is a classical marker of resident macrophages, including sNAMs, especially those originated from earlier precursors in the YS.[84,112,113] CX3CR1-expressing sNAMs are in close contact with the cell body of sensory neurons in the sensory ganglia, which constitutively express the membrane-bound CX3CL1.[213] The stimulation of the CX3CL1/CX3CR1 pathway in the dorsal horn of the spinal cord is a well-known mechanism involved in peripheral nerve injury–induced microglial activation/proliferation and neuropathic pain development.[34–36,213,237] Despite all the studies that indicated that the CX3CL1/CX3CR1 pathway in microglia plays a crucial role in neuropathic pain development,[124] none of these studies ruled out the possible role of this signaling in CX3CR1-expressing sNAMs of the sensory ganglia. In this context, after sciatic nerve injury or chemotherapy drug treatment, positive regulation of the CX3CL1/CX3CR1 axis in the sensory ganglia occurs.[28,30,213,237] Furthermore, after peripheral nerve injury, membrane-bound CX3CL1 is reduced in sensory neurons' cell

bodies, suggesting its release and action.[100,101] In fact, neutralization of CX3CL1 in the sensory ganglia reduced chemotherapy-induced neuropathic pain[81,218], which was associated with a reduction in the accumulation of sNAMs in the DRGs.[81] In addition, in vincristine-induced pain, another model of CIPN, macrophages, also accumulate in the sciatic nerve and promote pain hypersensitivity in a CX3CR1-dependent manner.[161] Therefore, the development of specific tools or approaches to investigate the particular contribution of the CX3CL1/CX3CR1 pathway in the spinal cord microglia or sNAMs in the periphery (eg, sensory ganglia or sciatic nerve) for the development of neuropathic pain are necessary.

The well-characterized chemokine that brings blood monocytes into inflamed tissues is CCL2.[116,204] This chemokine recruits monocytes/macrophages by activating its highly affinity CCR2 receptor.[67,185] This axis seems to play an essential role in the neuroinflammation process, including those associated with neuropathic pain development.[1,237] In fact, mice lacking CCL2 or CCR2 are resistant to the development of neuropathic pain caused by peripheral nerve injury. Furthermore, pharmacological inhibition of CCL2 and CCR2 with neutralizing antibody or antagonist, respectively, also attenuates mechanical allodynia induced by peripheral nerve injury.[53,227] Neutralization of the CCL2/CCR2 axis also protected from chemotherapy-induced neuropathic pain.[3,83] These studies strongly support the role of the CCL2/CCR2 axis in the development of some types of neuropathic pain. However, the mechanisms by which the CCL2/CCR2 axis mediates neuropathic pain development are not totally clear, but they might be multiples.[227] For instance, genetic or pharmacological inhibition of the CCL2/CCR2 pathway reduced monocytes accumulation in the sciatic nerve after traumatic nerve injury,[25,127,154,186] suggesting a peripheral effect. On the other hand, recent data did not show any change in the accumulation of sNAMs in the sensory ganglia after peripheral nerve injury,[235] indicating that the CCL2/CCR2 axis participates in the development of neuropathic pain would be preferentially at the local of the nerve injury. Supporting this hypothesis, perineural injection of CCL2 promotes pain hypersensitivity dependent on monocytes' recruitment.[40] Some studies suggest a possible role for the CCL2/CCR2 pathway in the spinal cord in the pathophysiology of neuropathic pain.[92,198] For instance, they demonstrated an increase in the expression of CCL2 by injured sensory neurons, which might be transported and released into the spinal cord, promoting the activation of CCR2-expressing glial cells.[209] However, it is striking that in CCR2-RFP mouse, a mouse strain in which CCR2-expressing cells also express red fluorescent protein, no significant detection of CCR2+ cells was observed in the spinal cord either in naive condition or after peripheral nerve injury.[68,71] There is also evidence suggesting CCL2 directly enhances primary sensory neurons excitability.[16,92,223] One significant problem to address the exact role of the CCL2/CCR2 axis in the development of neuropathic pain is the lack of specific tools, especially specific antibodies, to stain CCL2 and CCR2.

Furthermore, Ccr2 null mice have a defect to mobilize monocytes from the bone marrow; thus, even in naive conditions, these animals already have fewer monocytes in the bloodstream.[232] Noteworthy, double-blind clinical trials failed to demonstrate the efficacy of a selective and safe CCR2 antagonist in diabetes and posttraumatic neuropathic pain.[97,98] Therefore, further preclinical studies and clinical trials are necessary to further confirm the importance of the CCL2/CCR2 axis for neuropathic pain development and also the possible mechanisms underlying.[198,199]

Besides chemokines, cytokines' role in the activation/accumulation of sNAMs in the sensory ganglia after peripheral nerve injury was recently analyzed.[235] The specific knockdown of CSF1 in sensory neurons reduced macrophages activation/accumulation in DRGs after peripheral nerve injury and neuropathic pain.[235] These results indicated that the production/release of CSF1 by injured sensory neurons plays a crucial role in the direct sNAMs interaction that accounts for neuropathic pain development.

4.4. MicroRNAs and sensory neuron–associated macrophages

Studies report that after peripheral nerve injury, there is a robust dysregulation in the expression of noncoding RNAs, including microRNAs in sensory neurons.[12,114,153,174,189] For instance, it was found that activated or injured primary sensory neurons can release miR-21-5p as cargo in extracellular vesicles (eg, exosomes).[188] These sensory neuron–derived exosomes and their miR-21-5p cargo mediate sNAMs activation/accumulation in DRGs. In fact, after release, miR-21-5p in extracellular vesicles is readily captured by sNAMs in the DRG that, in turn, induces the polarization of sNAMs into a pronociceptive and proinflammatory phenotype.

Aside from these studies that provide several possible mechanisms involved in activation/accumulation of sNAMs in the sensory ganglia after peripheral nerve injury and, consequently, in developing neuropathic pain, further studies will be necessary to understand these crosstalks completely. For example, studies that conditionally knockdown molecular pathways or receptors in sNAMs would be required to further understand these interaction mechanisms.

4.5. Sensory neuron–associated macrophages effector mechanisms mediating neuropathic pain development

Based on the evidence we have described above, it is becoming clear that peripheral macrophages (eg, sNAMs of the sensory ganglia) participate in the pathophysiological process involved in the genesis of neuropathic pain of different subtypes. Of interest to the community is how peripheral macrophages reciprocally influence sensory neurons excitability after nerve injury that may contribute to these pathological states. Two main effector mechanisms have been attributed to peripheral macrophages at the local of nerve injury and sensory ganglia in the induction of neuropathic pain: (1) production of proinflammatory/nociceptive cytokines and (2) production of reactive oxygen species that in turn trigger TRPA1 stimulation.[6,15,27,149,211,234]

Resident sNAMs together with Schwann cells are the main source of the initial cytokines/chemokines cascade responsible for the recruitment of additional leukocytes, such as neutrophils, monocytes, and lymphocytes that infiltrate the local of nerve injury.[11,25,105,127] Besides promoting leukocytes recruitment, which amplify the inflammatory/immune process in the local nerve injury, these cytokines/chemokines may also directly enhance the excitability of primary sensory neurons.[159,191,217,218,223] Among cytokines produced/released by macrophages in the local of nerve injury that may affect directly and/or indirectly the excitability of primary nociceptive neurons, tumor necrosis factor (TNF), IL-1β, and IL-6 are well characterized.[53,56,125,159,177,191,217,223] Notably, the expression of proinflammatory cytokines in injured human nerve biopsies has been reported, and this response correlates with the degree of neuropathic pain.[129]

The activation phenotype of sNAMs in the sensory ganglia after peripheral nerve injury has been also associated with the production of proinflammatory cytokines.[235] We have shown that after spared nerve injury, the activation of NOD2 signaling in sNAMs mediates neuropathic pain development in a mechanism dependent on the production of TNF and IL-1β.[175] More recently, the CSF1/CSF1R signaling-dependent activation of sNAMs also triggers neuropathic pain through the production of IL1b.[235] Finally, it was suggested that sNAMs-derived IL-1β stimulates brain-derived neurotrophic factor by primary sensory neurons as a possible mechanism involved in the development of neuropathic pain.[235] Nevertheless, it is striking that sensory neurons specific knockdown of brain-derived neurotrophic factor did not affect neuropathic pain development.[42] Thus, the role of sNAMs-derived IL-1β in the sensory ganglia for the development of neuropathic pain is still under debate. In this context, several studies have indicated that primary sensory neurons may express receptors for proinflammatory cytokines/chemokines, including for those peripheral macrophage–derived cytokines (eg, IL-1β, TNF, and IL-6 receptors).[131,138] Based on that, several studies have analysed the possible effects of these cytokines on the excitability of primary sensory neurons.[151,159] For example, both TNF and IL-1β are able to enhance the excitability of cultured primary sensory neurons in vitro. Nevertheless these results would be analysed with caution because normally cultures of primary sensory neurons also contain other cell subtypes such as SGCs, and these cells may also express receptors for these cytokines,[187] hindering the interpretation of the data. One possibility to confirm the specific role of cytokines/cytokines receptor signaling directly on sensory neurons is the development of conditional animals that lack the expression of these cytokines receptors only in pain fibers. In this context, the specific knockout of gp130, a subunit of IL-6 receptor in primary nociceptive neurons, did not affect the development of neuropathic pain, suggesting no role for a direct action of IL-6 on sensory neurons in neuropathic pain[8]. Furthermore, the deletion of Il1r1 exclusively in the population of TRPV1+ nociceptors prevented the development of pathological pain in models of arthritis and multiple sclerosis.[138] The future use of these Il1r1 conditional mice and the generation of TNF receptors conditional knockout mice in primary nociceptive neurons would be necessary to explore and confirm this possibility in models of neuropathic pain after peripheral nerve injury.

Another possible effector mechanism by which peripheral macrophages and sNAMs contribute for neuropathic pain development is through the production of ROS. For example, ROS produced by recruited monocytes into the peripheral injured nerves mediates neuropathic pain development.[40,203] In fact, the depletion of these cells by clodronate treatment was able to attenuate the levels of hydrogen peroxide in the injured tissue, as well as nociceptive behavior.[40,95] It also showed that monocyte-derived ROS signals through TRPA1 receptors triggering peripheral sensibilization.[7,23,40,203] Whereas monocytes recruitment to the site of nerve injury that increase ROS production is dependent on CCL2/CCR2 signaling, there is evidence that macrophages/monocytes activation is dependent on ATR2 signaling[40,182,183] The sciatic nerve accumulated macrophages/monocytes also promote ROS production in CX3CR1-dependent manner and mediates vincristine-induced neuropathic pain.[161] There are several intracellular process and pathways that generate ROS, including mitochondria, xanthine oxidase, cytochrome P450 complexes, lipoxygenases, uncoupled endothelial nitric oxide synthase, and nicotinamide adenine dinucleotide phosphate oxidases. Nox-derived ROS has been implicated in the pathophysiology of neuropathic pain.[94,107] Notably, sNAMs of the sensory ganglia express Nox2 and increase the production of ROS after peripheral nerve injury.[96] Altogether these studies indicate that peripheral macrophage–derived ROS, including

Nox2 dependent, might be an interesting target for neuropathic pain control. Based on this hypothesis, pioglitazone, a PPARγ agonist, reduces cisplatin-induced neuropathic pain by reducing ROS production in the sensory ganglia.[102]

4.6. Sensory neuron–associated macrophages and resolution of neuropathic pain

Concomitantly to the production of pronociceptive molecules by immune and glial cells across the pain pathway (local of injury; sensory ganglia, and spinal cord) after peripheral nerve injury, there is also evidence suggesting the production of anti-inflammatory/antinociceptive molecules.[3,5,14,20,22,52,85,144,145,168,229] In this context, increasing evidence suggests that peripheral macrophages also play an important role in the resolution of chronic pain.[25,39] The identification of these regulatory mechanisms in peripheral macrophages that counteract neuropathic pain would also reveal novel targets for its treatment. For instance, we recently found that at the level of sensory ganglia there is an increase in the production of IL-27 which plays a regulatory role in the development of neuropathic pain.[52] We also showed that Il-27 counteracts neuropathic pain by acting on its receptor expressed by sNAMs that in turn stimulate the production of the antinociceptive cytokine IL-10.[52]

Endogenous cannabinoids produced in the periphery and the CNS are important components of endogenous analgesia.[5,109,150,168,172,212] For example, mice deficient in CB2 receptor showed enhanced pain hypersensitivity in models of neuropathic pain.[167] The mechanisms underlying the exacerbation of neuropathic pain in CB2 receptor null mice was recently investigated.[150] Notably, specific deletion of CB2 receptors in myeloid cells, especially in peripheral monocytes and sNAMs of the sensory ganglia, but not in neurons, also enhance neuropathic pain to the same level of whole-body deletion.[150] These results indicate that CB2 receptor signaling in peripheral macrophages limits the development of peripheral nerve injury–induced neuropathic pain. The mechanisms by which CB2R signaling modulates peripheral macrophages is not totally clear but seems to involve an increase in leptin signaling.[150,157] It could be also due to a reduction in the production of other pronociceptive mediators derived from peripheral macrophages. In fact, activation of CB2 receptors in macrophages reduced the production of proinflammatory cytokines (TNF and IL-1β) and ROS.[73,135] Thus, the development of CB2R agonists acting specifically in the periphery would be an interesting approach to target macrophages and to inhibit neuropathic pain development.

5. Conclusion remarks

In summary, this review pointed out the crucial participation of peripheral macrophages, especially sNAMs located in the sensory ganglia, for the development of neuropathic pain. It also described the cellular and molecular mechanisms involved in peripheral macrophages (eg, sensory ganglia sNAMs) activation/accumulation and effector functions after peripheral nerve injury that account for neuropathic pain development (**Fig.**
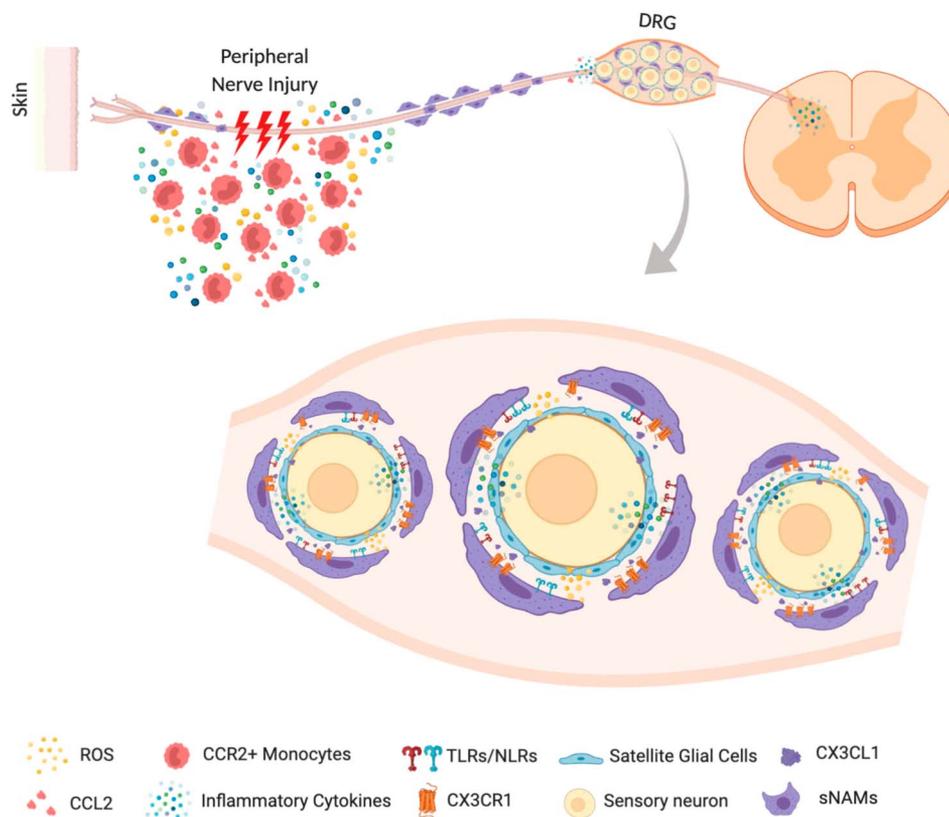

Figure 1. Representative illustration of the role of peripheral macrophages in the development of neuropathic pain. In the injured peripheral nerves, resident cells (Schwann cells, sNAMs) produced proinflammatory mediators, such as cytokines/chemokines which mediate the recruitment of additional leukocytes (eg, blood CCR2+ monocytes) and then more pronociceptive mediators are produced. This soup of proinflammatory cytokines amplifies the sensitization of primary sensory neurons and accounts for neuropathic pain development. In addition, after peripheral nerve injury, there is also accumulation/activation of sNAMs in the sensory ganglia. These cells also mediate the development of neuropathic pain through the production of cytokines (eg, IL-1β) and ROS. The possible molecular mechanisms involved in the activation of sNAMs in the sensory ganglia are also depicted. sNAMs, sensory neuron–associated macrophages.

1). In conclusion, these mechanisms could be explored as possible targets for the development of novel drugs to treat neuropathic pain.

Disclosures

References

[1] Abbadie C, Lindia JA, Cumiskey AM, Peterson LB, Mudgett JS, Bayne EK, DeMartino JA, MacIntyre DE, Forrest MJ. Impaired neuropathic pain responses in mice lacking the chemokine receptor CCR2. Proc Natl Acad Sci U S A 2003;100:7947–52.

[2] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006;124:783–801.

[3] Al-Mazidi S, Alotaibi M, Nedjadi T, Chaudhary A, Alzoghaibi M, Djouhri L. Blocking of cytokines signalling attenuates evoked and spontaneous neuropathic pain behaviours in the paclitaxel rat model of chemotherapy-induced neuropathy. Eur J Pain 2018;22:810–21.

[4] Amaral FA, Sachs D, Costa VV, Fagundes CT, Cisalpino D, Cunha TM, Ferreira SH, Cunha FQ, Silva TA, Nicoli JR, Vieira LQ, Souza DG, Teixeira MM. Commensal microbiota is fundamental for the development of inflammatory pain. Proc Natl Acad Sci U S A 2008;105:2193–7.

[5] Anand P, Whiteside G, Fowler CJ, Hohmann AG. Targeting CB2 receptors and the endocannabinoid system for the treatment of pain. Brain Res Rev 2009;60:255–66.

[6] Andersson DA, Gentry C, Moss S, Bevan S. Transient receptor potential A1 is a sensory receptor for multiple products of oxidative stress. J Neurosci 2008;28:2485–94.

[7] Andrade EL, Meotti FC, Calixto JB. TRPA1 antagonists as potential analgesic drugs. Pharmacol Ther 2012;133:189–204.

[8] Andratsch M, Mair N, Constantin CE, Scherbakov N, Benetti C, Quarta S, Vogl C, Sailer CA, Uceyler N, Brockhaus J, Martini R, Sommer C, Zeilhofer HU, Müller W, Kuner R, Davis JB, Rose-John S, Kress M. A key role for gp130 expressed on peripheral sensory nerves in pathological pain. J Neurosci 2009;29:13473–83.

[9] Arthur-Farraj PJ, Latouche M, Wilton DK, Quintes S, Chabrol E, Banerjee A, Woodhoo A, Jenkins B, Rahman M, Turmaine M, Wicher GK, Mitter R, Greensmith L, Behrens A, Raivich G, Mirsky R, Jessen KR. c-Jun reprograms Schwann cells of injured nerves to generate a repair cell essential for regeneration. Neuron 2012;75:633–47.

[10] Arvidson B. Cellular uptake of exogenous horseradish peroxidase in mouse peripheral nerve. Acta Neuropathol 1977;37:35–41.

[11] Austin PJ, Moalem-Taylor G. The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. J Neuroimmunol 2010;229:26–50.

[12] Bali KK, Selvaraj D, Satagopam VP, Lu J, Schneider R, Kuner R. Genome-wide identification and functional analyses of microRNA signatures associated with cancer pain. EMBO Mol Med 2013;5:1740–58.

[13] Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell 2009;139:267–84.

[14] Batten M, Li J, Yi S, Kljavin NM, Danilenko DM, Lucas S, Lee J, de Sauvage FJ, Ghilardi N. Interleukin 27 limits autoimmune encephalomyelitis by suppressing the development of interleukin 17-producing T cells. Nat Immunol 2006;7:929–36.

[15] 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.

[16] Belkouch M, Dansereau MA, Réaux-Le Goazigo A, Van Steenwinckel J, Beaudet N, Chraibi A, Melik-Parsadaniantz S, Sarret P. The chemokine CCL2 increases Nav1.8 sodium channel activity in primary sensory neurons through a Gβγ-dependent mechanism. J Neurosci 2011;31:18381–90.

[17] Bettoni I, Comelli F, Rossini C, Granucci F, Giagnoni G, Peri F, Costa B. Glial TLR4 receptor as new target to treat neuropathic pain: efficacy of a new receptor antagonist in a model of peripheral nerve injury in mice. Glia 2008;56:1312–9.

[18] Bevan MD, Wilson CJ. Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. J Neurosci 1999;19:7617–28.

[19] Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 2007;81:1–5.

[20] Bobinski F, Teixeira JM, Sluka KA, Santos ARS. Interleukin-4 mediates the analgesia produced by low-intensity exercise in mice with neuropathic pain. PAIN 2018;159:437–50.

[21] Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. PAIN 2008;136:380–7.

[22] Bráz JM, Basbaum AI. Differential ATF3 expression in dorsal root ganglion neurons reveals the profile of primary afferents engaged by diverse noxious chemical stimuli. PAIN 2010;150:290–301.

[23] Bruno K, Woller SA, Miller YI, Yaksh TL, Wallace M, Beaton G, Chakravarthy K. Targeting toll-like receptor-4 (TLR4)-an emerging therapeutic target for persistent pain states. PAIN 2018;159:1908–15.

[24] Burnett SH, Kershen EJ, Zhang J, Zeng L, Straley SC, Kaplan AM, Cohen DA. Conditional macrophage ablation in transgenic mice expressing a Fas-based suicide gene. J Leukoc Biol 2004;75:612–23.

[25] Calvo M, Dawes JM, Bennett DL. The role of the immune system in the generation of neuropathic pain. Lancet Neurol 2012;11:629–42.

[26] Cao L, Tanga FY, Deleo JA. The contributing role of CD14 in toll-like receptor 4 dependent neuropathic pain. Neuroscience 2009;158:896–903.

[27] Caspani O, Zurborg S, Labuz D, Heppenstall PA. The contribution of TRPM8 and TRPA1 channels to cold allodynia and neuropathic pain. PLoS One 2009;4:e7383.

[28] Chapman GA, Moores K, Harrison D, Campbell CA, Stewart BR, Strijbos PJ. Fractalkine cleavage from neuronal membranes represents an acute event in the inflammatory response to excitotoxic brain damage. J Neurosci 2000;20:RC87.

[29] Chauhan VS, Sterka DG Jr, Furr SR, Young AB, Marriott I. NOD2 plays an important role in the inflammatory responses of microglia and astrocytes to bacterial CNS pathogens. Glia 2009;57:414–23.

[30] Chen G, Park CK, Xie RG, Ji RR. Intrathecal bone marrow stromal cells inhibit neuropathic pain via TGF-β secretion. J Clin Invest 2015;125:3226–40.

[31] Cho IH, Lee MJ, Jang M, Gwak NG, Lee KY, Jung HS. Minocycline markedly reduces acute visceral nociception via inhibiting neuronal ERK phosphorylation. Mol Pain 2012;8:13.

[32] Clark AK, Malcangio M. Microglial signalling mechanisms: cathepsin S and fractalkine. Exp Neurol 2012;234:283–92.

[33] Clark AK, Malcangio M. Fractalkine/CX3CR1 signaling during neuropathic pain. Front Cell Neurosci 2014;8:121.

[34] Clark AK, Yip PK, Grist J, Gentry C, Staniland AA, Marchand F, Dehvari M, Wotherspoon G, Winter J, Ullah J, Bevan S, Malcangio M. Inhibition of spinal microglial cathepsin S for the reversal of neuropathic pain. Proc Natl Acad Sci U S A 2007;104:10655–60.

[35] Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med 2010;16:228–31.

[36] Cobos EJ, Nickerson CA, Gao F, Chandran V, Bravo-Caparrós I, González-Cano R, Riva P, Andrews NA, Latremoliere A, Seehus CR, Perazzoli G, Nieto FR, Joller N, Painter MW, Ma CHE, Omura T, Chesler EJ, Geschwind DH, Coppola G, Rangachari M, Woolf CJ, Costigan M. Mechanistic differences in neuropathic pain modalities revealed by correlating behavior with global expression profiling. Cell Rep 2018;22:1301–12.

[37] Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, Freeman R, Truini A, Attal N, Finnerup NB, Eccleston C, Kalso E, Bennett DL, Dworkin RH, Raja SN. Neuropathic pain. Nat Rev Dis Primers 2017;3:17002.

[38] Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 2006;29:1518–22.

[39] De Aquino MT, Kapil P, Hinton DR, Phares TW, Puntambekar SS, Savarin C, Bergmann CC, Stohlman SA. IL-27 limits central nervous

system viral clearance by promoting IL-10 and enhances demyelination. J Immunol 2014;193:285–94.

[40] De Logu F, Nassini R, Materazzi S, Carvalho Gonçalves M, Nosi D, Rossi Degl'Innocenti D, Marone IM, Ferreira J, Li Puma S, Benemei S, Trevisan G, Souza Monteiro de Araújo D, Patacchini R, Bunnett NW, Geppetti P. Schwann cell TRPA1 mediates neuroinflammation that sustains macrophage-dependent neuropathic pain in mice. Nat Commun 2017;8:1887.

[41] De Schepper S, Verheijden S, Aguilera-Lizarraga J, Viola MF, Boesmans W, Stakenborg N, Voytyuk I, Schmidt I, Boeckx B, Dierckx de Casterlé I, Baekelandt V, Gonzalez Dominguez E, Mack M, Depoortere I, De Strooper B, Sprangers B, Himmelreich U, Soenen S, Guilliams M, Vanden Berghe P, Jones E, Lambrechts D, Boeckxstaens G. Self-Maintaining gut macrophages are essential for intestinal homeostasis [published correction appears in Cell. 2019 Jan 24;176(3):676]. Cell 2018;175:400–15.e13.

[42] Dembo T, Braz JM, Hamel KA, Kuhn JA, Basbaum AI. Primary afferent-derived BDNF contributes minimally to the processing of pain and itch. eNeuro 2018;5:ENEURO.0402–18.2018.

[43] Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. J Clin Invest 2010;120:3760–72.

[44] Duffield JS, Forbes SJ, Constandinou CM, Clay S, Partolina M, Vuthoori S, Wu S, Lang R, Iredale JP. Selective depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J Clin Invest 2005; 115:56–65.

[45] Elmore MR, Najafi AR, Koike MA, Dagher NN, Spangenberg EE, Rice RA, Kitazawa M, Matusow B, Nguyen H, West BL, Green KN. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. Neuron 2014; 82:380–97.

[46] England JD, Happel LT, Kline DG, Gamboni F, Thouron CL, Liu ZP, Levinson SR. Sodium channel accumulation in humans with painful neuromas. Neurology 1996;47:272–6.

[47] Esper RM, Loeb JA. Rapid axoglial signaling mediated by neuregulin and neurotrophic factors [published correction appears in J Neurosci. 2004 Jul 28;24(30):1 p following 6852]. J Neurosci 2004;24:6218–27.

[48] Felipe-Ribeiro FA, Verri WA, Jr, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. Trends Immunol 2017; 38:5–19.

[49] Ferreira SH, Romitelli M, de Nucci G. Endothelin-1 participation in overt and inflammatory pain. J Cardiovasc Pharmacol 1989;13(suppl 5): S220–2.

[50] Fitzgerald DC, Zhang GX, El-Behi M, Fonseca-Kelly Z, Li H, Yu S, Saris CJ, Gran B, Ciric B, Rostami A. Suppression of autoimmune inflammation of the central nervous system by interleukin 10 secreted by interleukin 27-stimulated T cells [published correction appears in Nat Immunol. 2008 Jan;9(1):105]. Nat Immunol 2007;8:1372–9.

[51] Flatters SJ, Fox AJ, Dickenson AH. Nerve injury alters the effects of interleukin-6 on nociceptive transmission in peripheral afferents. Eur J Pharmacol 2004;484:183–91.

[52] Fonseca MM, Davoli-Ferreira M, Santa-Cecília F, Guimarães RM, Oliveira FFB, Kusuda R, Ferreira DW, Alves-Filho JC, Cunha FQ, Cunha TM. IL-27 counteracts neuropathic pain development through induction of IL-10. Front Immunol 2020;10:3059.

[53] Gao YJ, Zhang L, Samad OA, Suter MR, Yasuhiko K, Xu ZZ, Park JY, Lind AL, Ma Q, Ji RR. JNK-induced MCP-1 production in spinal cord astrocytes contributes to central sensitization and neuropathic pain. J Neurosci 2009;29:4096–108.

[54] Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. J Neuroinflammation 2011;8:110.

[55] Gehrmann J, Monaco S, Kreutzberg GW. Spinal cord microglial cells and DRG satellite cells rapidly respond to transection of the rat sciatic nerve. Restor Neurol Neurosci 1991;2:181–98.

[56] Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells [published correction appears in Science. 2010 Dec 3;330(6009): 1319]. Science 2010;327:656–61.

[57] Ghasemlou N, Chiu IM, Julien JP, Woolf CJ. CD11b+Ly6G- myeloid cells mediate mechanical inflammatory pain hypersensitivity. Proc Natl Acad Sci U S A 2015;112:E6808–17.

[58] Ginhoux F, Guilliams M. Tissue-resident macrophage ontogeny and homeostasis. Immunity 2016;44:439–49.

[59] Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM, Merad M. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 2010;330:841–5.

[60] Ginhoux F, Schultze JL, Murray PJ, Ochando J, Biswas SK. New insights into the multidimensional concept of macrophage ontogeny, activation and function. Nat Immunol 2016;17:34–40.

[61] Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med 2010;16:1248–57.

[62] Goldmann T, Wieghofer P, Jordão MJ, Prutek F, Hagemeyer N, Frenzel K, Amann L, Staszewski O, Kierdorf K, Krueger M, Locatelli G, Hochgerner H, Zeiser R, Epelman S, Geissmann F, Priller J, Rossi FM, Bechmann I, Kerschensteiner M, Linnarsson S, Jung S, Prinz M. Origin, fate and dynamics of macrophages at central nervous system interfaces. Nat Immunol 2016;17:797–805.

[63] Gomez Perdiguero E, Klapproth K, Schulz C, Busch K, Azzoni E, Crozet L, Garner H, Trouillet C, de Bruijn MF, Geissmann F, Rodewald HR. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. Nature 2015;518:547–51.

[64] Goren I, Allmann N, Yogev N, Schürmann C, Linke A, Holdener M, Waisman A, Pfeilschifter J, Frank S. A transgenic mouse model of inducible macrophage depletion: effects of diphtheria toxin-driven lysozyme M-specific cell lineage ablation on wound inflammatory, angiogenic, and contractive processes. Am J Pathol 2009;175:132–47.

[65] Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. Nat Rev Immunol 2014;14:217–31.

[66] Grothe C, Heese K, Meisinger C, Wewetzer K, Kunz D, Cattini P, Otten U. Expression of interleukin-6 and its receptor in the sciatic nerve and cultured Schwann cells: relation to 18-kD fibroblast growth factor-2. Brain Res 2000;885:172–81.

[67] Gschwandtner M, Derler R, Midwood KS. More than just attractive: how CCL2 influences myeloid cell behavior beyond chemotaxis. Front Immunol 2019;10:2759.

[68] Gu N, Peng J, Murugan M, Wang X, Eyo UB, Sun D, Ren Y, DiCicco-Bloom E, Young W, Dong H, Wu LJ. Spinal microgliosis due to resident microglial proliferation is required for pain hypersensitivity after peripheral nerve injury. Cell Rep 2016;16:605–14.

[69] Guedes RP, Araújo AS, Janner D, Belló-Klein A, Ribeiro MF, Partata WA. Increase in reactive oxygen species and activation of Akt signaling pathway in neuropathic pain. Cell Mol Neurobiol 2008;28:1049–56.

[70] Guilliams M, Mildner A, Yona S. Developmental and functional heterogeneity of monocytes. Immunity 2018;49:595–613.

[71] Guimarães RM, Davoli-Ferreira M, Fonseca MM, Damasceno LEA, Santa-Cecília FV, Kusuda R, Menezes GB, Cunha FQ, Alves-Filho JC, Cunha TM. Frontline Science: blood-circulating leukocytes fail to infiltrate the spinal cord parenchyma after spared nerve injury. J Leukoc Biol 2019;106:541–51.

[72] Guo LH, Guo KT, Wendel HP, Schluesener HJ. Combinations of TLR and NOD2 ligands stimulate rat microglial P2X4R expression. Biochem Biophys Res Commun 2006;349:1156–62.

[73] Han KH, Lim S, Ryu J, Lee CW, Kim Y, Kang JH, Kang SS, Ahn YK, Park CS, Kim JJ. CB1 and CB2 cannabinoid receptors differentially regulate the production of reactive oxygen species by macrophages. Cardiovasc Res 2009;84:378–86.

[74] Haroutounian S, Nikolajsen L, Bendtsen TF, Finnerup NB, Kristensen AD, Hasselstrøm JB, Jensen TS. Primary afferent input critical for maintaining spontaneous pain in peripheral neuropathy. PAIN 2014; 155:1272–9.

[75] Hasegawa M, Fujimoto Y, Lucas PC, Nakano H, Fukase K, Núñez G, Inohara N. A critical role of RICK/RIP2 polyubiquitination in Nod-induced NF-kappaB activation. EMBO J 2008;27:373–83.

[76] Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, Becker CD, See P, Price J, Lucas D, Greter M, Mortha A, Boyer SW, Forsberg EC, Tanaka M, van Rooijen N, García-Sastre A, Stanley ER, Ginhoux F, Frenette PS, Merad M. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity 2013;38:792–804.

[77] Helgason S, Petursson G, Gudmundsson S, Sigurdsson JA. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ 2000;321:794–6.

[78] Hill RZ, Bautista DM. Getting in touch with mechanical pain mechanisms. Trends Neurosci 2020;43:311–25.

[79] Hoeffel G, Chen J, Lavin Y, Almeida FF, See P, Beaudin AE, Lum J, Low I, Forsberg EC, Poidinger M, Zolezzi F, Larbi A, Ng LG, Chan JK, Greter M, Becher B, Samokhvalov IM, Merad M, Ginhoux F. C-Myb(+) erythro-myeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. Immunity 2015;42:665–78.

[80] Hu P, McLachlan EM. Distinct functional types of macrophage in dorsal root ganglia and spinal nerves proximal to sciatic and spinal nerve transections in the rat. Exp Neurol 2003;184:590–605.

[81] Huang ZZ, Li D, Liu CC, Cui Y, Zhu HQ, Zhang WW, Li YY, Xin WJ. CX3CL1-mediated macrophage activation contributed to paclitaxel-

induced DRG neuronal apoptosis and painful peripheral neuropathy. Brain Behav Immun 2014;40:155–65.

[82] Ibrahim MM, Deng H, Zvonok A, Cockayne DA, Kwan J, Mata HP, Vanderah TW, Lai J, Porreca F, Makriyannis A, Malan TP. Activation of CB2 cannabinoid receptors by AM1241 inhibits experimental neuropathic pain: pain inhibition by receptors not present in the CNS. Proc Natl Acad Sci U S A 2003;100:10529–33.

[83] Illias AM, Gist AC, Zhang H, Kosturakis AK, Dougherty PM. Chemokine CCL2 and its receptor CCR2 in the dorsal root ganglion contribute to oxaliplatin-induced mechanical hypersensitivity. PAIN 2018;159: 1308–16.

[84] Ishida Y, Gao JL, Murphy PM. Chemokine receptor CX3CR1 mediates skin wound healing by promoting macrophage and fibroblast accumulation and function. J Immunol 2008;180:569–79.

[85] Jancálek R, Dubový P, Svízenská I, Klusáková I. Bilateral changes of TNF-alpha and IL-10 protein in the lumbar and cervical dorsal root ganglia following a unilateral chronic constriction injury of the sciatic nerve. J Neuroinflammation 2010;7:11.

[86] Ji RR, Strichartz G. Cell signaling and the genesis of neuropathic pain. Sci STKE 2004;2004:reE14.

[87] Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov 2014;13:533–48.

[88] Ji RR, Chamessian A, Zhang YQ. Pain regulation by non-neuronal cells and inflammation. Science 2016;354:572–7.

[89] Jimenez-Andrade JM, Peters CM, Mejia NA, Ghilardi JR, Kuskowski MA, Mantyh PW. Sensory neurons and their supporting cells located in the trigeminal, thoracic and lumbar ganglia differentially express markers of injury following intravenous administration of paclitaxel in the rat. Neurosci Lett 2006;405:62–7.

[90] Joosten LA, Heinhuis B, Abdollahi-Roodsaz S, Ferwerda G, Lebourhis L, Philpott DJ, Nahori MA, Popa C, Morre SA, van der Meer JW, Girardin SE, Netea MG, van den Berg WB. Differential function of the NACHT-LRR (NLR) members Nod1 and Nod2 in arthritis. Proc Natl Acad Sci U S A 2008;105:9017–22.

[91] Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature 2001;413:203–10.

[92] Jung H, Toth PT, White FA, Miller RJ. Monocyte chemoattractant protein-1 functions as a neuromodulator in dorsal root ganglia neurons. J Neurochem 2008;104:254–63.

[93] Jung H, Bhangoo S, Banisadr G, Freitag C, Ren D, White FA, Miller RJ. Visualization of chemokine receptor activation in transgenic mice reveals peripheral activation of CCR2 receptors in states of neuropathic pain. J Neurosci 2009;29:8051–62.

[94] Kallenborn-Gerhardt W, Schröder K, Del Turco D, Lu R, Kynast K, Kosowski J, Niederberger E, Shah AM, Brandes RP, Geisslinger G, Schmidtko A. NADPH oxidase-4 maintains neuropathic pain after peripheral nerve injury. J Neurosci 2012;32:10136–45.

[95] Kallenborn-Gerhardt W, Lu R, Syhr KM, Heidler J, von Melchner H, Geisslinger G, Bangsow T, Schmidtko A. Antioxidant activity of sestrin 2 controls neuropathic pain after peripheral nerve injury. Antioxid Redox Signal 2013;19:2013–23.

[96] Kallenborn-Gerhardt W, Hohmann SW, Syhr KM, Schröder K, Sisignano M, Weigert A, Lorenz JE, Lu R, Brüne B, Brandes RP, Geisslinger G, Schmidtko A. Nox2-dependent signaling between macrophages and sensory neurons contributes to neuropathic pain hypersensitivity. PAIN 2014;155:2161–70.

[97] Kalliomäki J, Attal N, Jonzon B, Bach FW, Huizar K, Ratcliffe S, Eriksson B, Janecki M, Danilov A, Bouhassira D. A randomized, double-blind, placebo-controlled trial of a chemokine receptor 2 (CCR2) antagonist in posttraumatic neuralgia. PAIN 2013;154:761–7.

[98] Kalliomäki J, Jonzon B, Huizar K, O'Malley M, Andersson A, Simpson DM. Evaluation of a novel chemokine receptor 2 (CCR2)-antagonist in painful diabetic polyneuropathy. Scand J Pain 2013;4:77–83.

[99] Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nat Rev Immunol 2013;13:321–35.

[100] Katsura H, Obata K, Mizushima T, Yamanaka H, Kobayashi K, Dai Y, Fukuoka T, Tokunaga A, Sakagami M, Noguchi K. Antisense knock down of TRPA1, but not TRPM8, alleviates cold hyperalgesia after spinal nerve ligation in rats. Exp Neurol 2006;200:112–23.

[101] Khan J, Ramadan K, Korczeniewska O, Anwer MM, Benoliel R, Eliav E. Interleukin-10 levels in rat models of nerve damage and neuropathic pain. Neurosci Lett 2015;592:99–106.

[102] Khasabova IA, Khasabov SG, Olson JK, Uhelski ML, Kim AH, Albino-Ramírez AM, Wagner CL, Seybold VS, Simone DA. Pioglitazone, a PPARγ agonist, reduces cisplatin-evoked neuropathic pain by protecting against oxidative stress. PAIN 2019;160:688–701.

[103] Kigerl KA, Hall JC, Wang L, Mo X, Yu Z, Popovich PG. Gut dysbiosis impairs recovery after spinal cord injury. J Exp Med 2016;213:2603–20.

[104] Kiguchi N, Maeda T, Kobayashi Y, Kondo T, Ozaki M, Kishioka S. The critical role of invading peripheral macrophage-derived interleukin-6 in vincristine-induced mechanical allodynia in mice. Eur J Pharmacol 2008;592:87–92.

[105] Kim CF, Moalem-Taylor G. Detailed characterization of neuro-immune responses following neuropathic injury in mice. Brain Res 2011;1405: 95–108.

[106] Kim HK, Park SK, Zhou JL, Taglialatela G, Chung K, Coggeshall RE, Chung JM. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. PAIN 2004;111:116–24.

[107] Kim D, You B, Jo EK, Han SK, Simon MI, Lee SJ. NADPH oxidase 2-derived reactive oxygen species in spinal cord microglia contribute to peripheral nerve injury-induced neuropathic pain. Proc Natl Acad Sci U S A 2010;107:14851–6.

[108] Kim D, You B, Lim H, Lee SJ. Toll-like receptor 2 contributes to chemokine gene expression and macrophage infiltration in the dorsal root ganglia after peripheral nerve injury. Mol Pain 2011;7:74.

[109] Kinsey SG, Long JZ, O'Neal ST, Abdullah RA, Poklis JL, Boger DL, Cravatt BF, Lichtman AH. Blockade of endocannabinoid-degrading enzymes attenuates neuropathic pain. J Pharmacol Exp Ther 2009;330: 902–10.

[110] Klit H, Finnerup NB, Andersen G, Jensen TS. Central poststroke pain: a population-based study. PAIN 2011;152:818–24.

[111] Kobayashi K, Inohara N, Hernandez LD, Galán JE, Núñez G, Janeway CA, Medzhitov R, Flavell RA. RICK/Rip2/CARDIAK mediates signalling for receptors of the innate and adaptive immune systems. Nature 2002; 416:194–9.

[112] Kolter J, Feuerstein R, Zeis P, Hagemeyer N, Paterson N, d'Errico P, Baasch S, Amann L, Masuda T, Lösslein A, Gharun K, Meyer-Luehmann M, Waskow C, Franzke CW, Grün D, Lämmermann T, Prinz M, Henneke P. A subset of skin macrophages contributes to the surveillance and regeneration of local nerves. Immunity 2019;50: 1482–e7.

[113] Kolter J, Kierdorf K, Henneke P. Origin and differentiation of nerve-associated macrophages. J Immunol 2020;204:271–9.

[114] Kress M, Hüttenhofer A, Landry M, Kuner R, Favereaux A, Greenberg D, Bednarik J, Heppenstall P, Kronenberg F, Malcangio M, Rittner H, Uçeyler N, Trajanoski Z, Mouritzen P, Birklein F, Sommer C, Soreq H. microRNAs in nociceptive circuits as predictors of future clinical applications. Front Mol Neurosci 2013;6:33.

[115] Krueger JM, Karnovsky ML, Martin SA, Pappenheimer JR, Walter J, Biemann K. Peptidoglycans as promoters of slow-wave sleep. II. Somnogenic and pyrogenic activities of some naturally occurring muramyl peptides; correlations with mass spectrometric structure determination. J Biol Chem 1984;259:12659–62.

[116] Kurihara T, Warr G, Loy J, Bravo R. Defects in macrophage recruitment and host defense in mice lacking the CCR2 chemokine receptor. J Exp Med 1997;186:1757–62.

[117] Kwon MJ, Kim J, Shin H, Jeong SR, Kang YM, Choi JY, Hwang DH, Kim BG. Contribution of macrophages to enhanced regenerative capacity of dorsal root ganglia sensory neurons by conditioning injury. J Neurosci 2013;33:15095–108.

[118] Kwon MJ, Shin HY, Cui Y, Kim H, Thi AH, Choi JY, Kim EY, Hwang DH, Kim BG. CCL2 mediates neuron-macrophage interactions to drive proregenerative macrophage activation following preconditioning injury. J Neurosci 2015;35:15934–47.

[119] Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. Pharmacol Rev 2001;53:597–652.

[120] Lee YK, Menezes JS, Umesaki Y, Mazmanian SK. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc Natl Acad Sci U S A 2011;108(suppl 1): 4615–22.

[121] Lee S, Shi XQ, Fan A, West B, Zhang J. Targeting macrophage and microglia activation with colony stimulating factor 1 receptor inhibitor is an effective strategy to treat injury-triggered neuropathic pain. Mol Pain 2018;14:1744806918764979.

[122] Li Y, Zhang H, Zhang H, Kosturakis AK, Jawad AB, Dougherty PM. Toll-like receptor 4 signaling contributes to Paclitaxel-induced peripheral neuropathy. J Pain 2014;15:712–25.

[123] Li Y, Zhang H, Kosturakis AK, Cassidy RM, Zhang H, Kennamer-Chapman RM, Jawad AB, Colomand CM, Harrison DS, Dougherty PM. MAPK signaling downstream to TLR4 contributes to paclitaxel-induced peripheral neuropathy. Brain Behav Immun 2015;49:255–66.

[124] Li D, Chen H, Luo XH, Sun Y, Xia W, Xiong YC. CX3CR1-Mediated Akt1 activation contributes to the paclitaxel-induced painful peripheral neuropathy in rats. Neurochem Res 2016;41:1305–14.

[125] Li QY, Xu HY, Yang HJ. Effect of proinflammatory factors TNF-α, IL-1β, IL-6 on neuropathic pain [in Chinese]. Zhongguo Zhong Yao Za Zhi 2017;42(19):3709–12.

[126] Lim H, Lee J, You B, Oh JH, Mok HJ, Kim YS, Yoon BE, Kim BG, Back SK, Park JS, Kim KP, Schnaar RL, Lee SJ. GT1b functions as a novel endogenous agonist of toll-like receptor 2 inducing neuropathic pain. EMBO J 2020;39:e102214.

[127] Lindborg JA, Mack M, Zigmond RE. Neutrophils are critical for myelin removal in a peripheral nerve injury model of wallerian degeneration. J Neurosci 2017;37:10258–77.

[128] Lindborg JA, Niemi JP, Howarth MA, Liu KW, Moore CZ, Mahajan D, Zigmond RE. Molecular and cellular identification of the immune response in peripheral ganglia following nerve injury. J Neuroinflammation 2018;15:192.

[129] Lindenlaub T, Sommer C. Cytokines in sural nerve biopsies from inflammatory and non-inflammatory neuropathies. Acta Neuropathol 2003;105:593–602.

[130] Liu T, van Rooijen N, Tracey DJ. Depletion of macrophages reduces axonal degeneration and hyperalgesia following nerve injury. PAIN 2000; 86:25–32.

[131] Liu B, Li H, Brull SJ, Zhang JM. Increased sensitivity of sensory neurons to tumor necrosis factor alpha in rats with chronic compression of the lumbar ganglia. J Neurophysiol 2002;88:1393–9.

[132] 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.

[133] 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.

[134] Liu XJ, Liu T, Chen G, Wang B, Yu XL, Yin C, Ji RR. TLR signaling adaptor protein MyD88 in primary sensory neurons contributes to persistent inflammatory and neuropathic pain and neuroinflammation. Sci Rep 2016;6:28188.

[135] Liu AP, Yuan QH, Zhang B, Yang L, He QW, Chen K, Liu QS, Li Z, Zhan J. Cannabinoid receptor 2 activation alleviates septic lung injury by promoting autophagy via inhibition of inflammatory mediator release [published correction appears in Cell Signal. 2020 Aug;72:109600]. Cell Signal 2020;69:109556.

[136] Loeser JD, Treede RD. The kyoto protocol of IASP basic pain terminology. PAIN 2008;137:473–7.

[137] Luo X, Huh Y, Bang S, He Q, Zhang L, Matsuda M, Ji RR. Macrophage toll-like receptor 9 contributes to chemotherapy-induced neuropathic pain in male mice. J Neurosci 2019;39:6848–64.

[138] Mailhot B, Christin M, Tessandier N, Sotoudeh C, Bretheau F, Turmel R, Pellerin È, Wang F, Bories C, Joly-Beauparlant C, De Koninck Y, Droit A, Cicchetti F, Scherrer G, Boilard E, Sharif-Naeini R, Lacroix S. Neuronal interleukin-1 receptors mediate pain in chronic inflammatory diseases. J Exp Med 2020;217:e20191430.

[139] Makker PG, Duffy SS, Lees JG, Perera CJ, Tonkin RS, Butovsky O, Park SB, Goldstein D, Moalem-Taylor G. Characterisation of immune and neuroinflammatory changes associated with chemotherapy-induced peripheral neuropathy. PLoS One 2017;12:e0170814.

[140] Marin IA, Goertz JE, Ren T, Rich SS, Onengut-Gumuscu S, Farber E, Wu M, Overall CC, Kipnis J, Gaultier A. Microbiota alteration is associated with the development of stress-induced despair behavior. Sci Rep 2017; 7:43859.

[141] Materazzi S, Fusi C, Benemei S, Pedretti P, Patacchini R, Nilius B, Prenen J, Creminon C, Geppetti P, Nassini R. TRPA1 and TRPV4 mediate paclitaxel-induced peripheral neuropathy in mice via a glutathione-sensitive mechanism. Pflugers Arch 2012;463:561–9.

[142] McGrath KE, Frame JM, Fegan KH, Bowen JR, Conway SJ, Catherman SC, Kingsley PD, Koniski AD, Palis J. Distinct sources of hematopoietic progenitors emerge before HSCs and provide functional blood cells in the mammalian embryo. Cell Rep 2015;11:1892–904.

[143] Melief MJ, Hoijer MA, Van Paassen HC, Hazenberg MP. Presence of bacterial flora-derived antigen in synovial tissue macrophages and dendritic cells. Br J Rheumatol 1995;34:1112–6.

[144] Milligan ED, Langer SJ, Sloane EM, He L, Wieseler-Frank J, O'Connor K, Martin D, Forsayeth JR, Maier SF, Johnson K, Chavez RA, Leinwand LA, Watkins LR. Controlling pathological pain by adenovirally driven spinal production of the anti-inflammatory cytokine, interleukin-10. Eur J Neurosci 2005;21:2136–48.

[145] Milligan ED, Penzkover KR, Soderquist RG, Mahoney MJ. Spinal interleukin-10 therapy to treat peripheral neuropathic pain. Neuromodulation 2012;15:520–6.

[146] Montague K, Simeoli R, Valente J, Malcangio M. A novel interaction between CX3CR1 and CCR2 signalling in monocytes constitutes an underlying mechanism for persistent vincristine-induced pain. J Neuroinflammation 2018;15:101.

[147] Mueller M, Wacker K, Ringelstein EB, Hickey WF, Imai Y, Kiefer R. Rapid response of identified resident endoneurial macrophages to nerve injury. Am J Pathol 2001;159:2187–97.

[148] Nassini R, Gees M, Harrison S, De Siena G, Materazzi S, Moretto N, Failli P, Preti D, Marchetti N, Cavazzini A, Mancini F, Pedretti P, Nilius B, Patacchini R, Geppetti P. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. PAIN 2011;152: 1621–31.

[149] Nassini R, Materazzi S, Benemei S, Geppetti P. The TRPA1 channel in inflammatory and neuropathic pain and migraine. Rev Physiol Biochem Pharmacol 2014;167:1–43.

[150] Nent E, Nozaki C, Schmöle AC, Otte D, Zimmer A. CB2 receptor deletion on myeloid cells enhanced mechanical allodynia in a mouse model of neuropathic pain. Sci Rep 2019;9:7468.

[151] Nicol GD, Lopshire JC, Pafford CM. Tumor necrosis factor enhances the capsaicin sensitivity of rat sensory neurons. J Neurosci 1997;17: 975–82.

[152] Nicotra L, Loram LC, Watkins LR, Hutchinson MR. Toll-like receptors in chronic pain. Exp Neurol 2012;234:316–29.

[153] Niederberger E, Kynast K, Lötsch J, Geisslinger G. MicroRNAs as new players in the pain game. PAIN 2011;152:1455–8.

[154] Niemi JP, DeFrancesco-Lisowitz A, Roldán-Hernández L, Lindborg JA, Mandell D, Zigmond RE. A critical role for macrophages near axotomized neuronal cell bodies in stimulating nerve regeneration. J Neurosci 2013;33:16236–48.

[155] Ninoue K. The function of microglia through purinergic receptors: neuropathic pain and cytokine release. Pharmacol Ther 2006;109: 210–26.

[156] Noverr MC, Huffnagle GB. Does the microbiota regulate immune responses outside the gut?. Trends Microbiol 2004;12:562–8.

[157] Nozaki C, Nent E, Bilkei-Gorzo A, Zimmer A. Involvement of leptin signaling in the development of cannabinoid CB2 receptor-dependent mirror image pain. Sci Rep 2018;8:10827.

[158] Obata K, Katsura H, Mizushima T, Yamanaka H, Kobayashi K, Dai Y, Fukuoka T, Tokunaga A, Tominaga M, Noguchi K. TRPA1 induced in sensory neurons contributes to cold hyperalgesia after inflammation and nerve injury [published correction appears in J Clin Invest. 2010 Jan; 120(1):394]. J Clin Invest 2005;115:2393–401.

[159] Obreja O, Rathee PK, Lips KS, Distler C, Kress M. IL-1 beta potentiates heat-activated currents in rat sensory neurons: involvement of IL-1RI, tyrosine kinase, and protein kinase C. FASEB J 2002;16:1497–503.

[160] Okabe Y, Medzhitov R. Tissue biology perspective on macrophages. Nat Immunol 2016;17:9–17.

[161] Old EA, Nadkarni S, Grist J, Gentry C, Bevan S, Kim KW, Mogg AJ, Perretti M, Malcangio M. Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. J Clin Invest 2014;124: 2023–36.

[162] Oldfors A. Macrophages in peripheral nerves. An ultrastructural and enzyme histochemical study on rats. Acta Neuropathol 1980;49:43–9.

[163] Park CK, Xu ZZ, Berta T, Han Q, Chen G, Liu XJ, Ji RR. Extracellular microRNAs activate nociceptor neurons to elicit pain via TLR7 and TRPA1. Neuron 2014;82:47–54.

[164] Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR, Lafaille JJ, Hempstead BL, Littman DR, Gan WB. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 2013;155:1596–609.

[165] Peng J, Gu N, Zhou L, B Eyo U, Murugan M, Gan WB, Wu LJ. Microglia and monocytes synergistically promote the transition from acute to chronic pain after nerve injury. Nat Commun 2016;7:12029.

[166] Perdiguero EG, Geissmann F. The development and maintenance of resident macrophages. Nat Immunol 2016;17:2–8.

[167] Racz I, Nadal X, Alferink J, Baños JE, Rehnelt J, Martín M, Pintado B, Gutierrez-Adan A, Sanguino E, Manzanares J, Zimmer A, Maldonado R. Crucial role of CB(2) cannabinoid receptor in the regulation of central immune responses during neuropathic pain. J Neurosci 2008;28: 12125–35.

[168] Rani Sagar D, Burston JJ, Woodhams SG, Chapman V. Dynamic changes to the endocannabinoid system in models of chronic pain. Philos Trans R Soc Lond B Biol Sci 2012;367:3300–11.

[169] Ransohoff RM, Liu L, Cardona AE. Chemokines and chemokine receptors: multipurpose players in neuroinflammation. Int Rev Neurobiol 2007;82:187–204.

[170] Ransohoff RM. Chemokines and chemokine receptors: standing at the crossroads of immunobiology and neurobiology. Immunity 2009;31: 711–21.

[171] Rollins BJ. Chemokines. Blood 1997;90:909–28.

[172] Romero-Sandoval EA, Horvath R, Landry RP, DeLeo JA. Cannabinoid receptor type 2 activation induces a microglial antiinflammatory

phenotype and reduces migration via MKP induction and ERK dephosphorylation. Mol Pain 2009;5:25.

[173] Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease [published correction appears in Nat Rev Immunol. 2009 Aug;9(8):600]. Nat Rev Immunol 2009;9: 313–23.

[174] Sakai A, Suzuki H. microRNA and Pain. Adv Exp Med Biol 2015;888: 17–39.

[175] Santa-Cecília FV, Ferreira DW, Guimaraes RM, Cecilio NT, Fonseca MM, Lopes AH, Davoli-Ferreira M, Kusuda R, Souza GR, Nachbur U, Alves-Filho JC, Teixeira MM, Zamboni DS, Cunha FQ, Cunha TM. The NOD2 signaling in peripheral macrophages contributes to neuropathic pain development. PAIN 2019;160:102–16.

[176] Sawada Y, Hosokawa H, Matsumura K, Kobayashi S. Activation of transient receptor potential ankyrin 1 by hydrogen peroxide. Eur J Neurosci 2008;27:1131–42.

[177] Schäfers M, Geis C, Brors D, Yaksh TL, Sommer C. Anterograde transport of tumor necrosis factor-alpha in the intact and injured rat sciatic nerve. J Neurosci 2002;22:536–45.

[178] Scholz J, Woolf CJ. The neuropathic pain triad: neurons, immune cells and glia. Nat Neurosci 2007;10:1361–8.

[179] Schulz C, Gomez Perdiguero E, Chorro L, Szabo-Rogers H, Cagnard N, Kierdorf K, Prinz M, Wu B, Jacobsen SE, Pollard JW, Frampton J, Liu KJ, Geissmann F. A lineage of myeloid cells independent of Myb and hematopoietic stem cells. Science 2012;336:86–90.

[180] Shen S, Lim G, You Z, Ding W, Huang P, Ran C, Doheny J, Caravan P, Tate S, Hu K, Kim H, McCabe M, Huang B, Xie Z, Kwon D, Chen L, Mao J. Gut microbiota is critical for the induction of chemotherapy-induced pain. Nat Neurosci 2017;20:1213–16.

[181] Sheng J, Ruedl C, Karjalainen K. Most tissue-resident macrophages except microglia are derived from fetal hematopoietic stem cells. Immunity 2015;43:382–93.

[182] Shepherd AJ, Copits BA, Mickle AD, Karlsson P, Kadunganattil S, Haroutounian S, Tadinada SM, de Kloet AD, Valtcheva MV, McIlvried LA, Sheahan TD, Jain S, Ray PR, Usachev YM, Dussor G, Krause EG, Price TJ, Gereau RW, Mohapatra DP. Angiotensin II triggers peripheral macrophage-to-sensory neuron redox crosstalk to elicit pain. J Neurosci 2018;38:7032–57.

[183] Shepherd AJ, Mickle AD, Golden JP, Mack MR, Halabi CM, de Kloet AD, Samineni VK, Kim BS, Krause EG, Gereau RW, Mohapatra DP. Macrophage angiotensin II type 2 receptor triggers neuropathic pain. Proc Natl Acad Sci U S A 2018;115:E8057–66.

[184] Shi XQ, Zekki H, Zhang J. The role of TLR2 in nerve injury-induced neuropathic pain is essentially mediated through macrophages in peripheral inflammatory response. Glia 2011;59:231–41.

[185] Si Y, Tsou CL, Croft K, Charo IF. CCR2 mediates hematopoietic stem and progenitor cell trafficking to sites of inflammation in mice. J Clin Invest 2010;120:1192–203.

[186] Siebert H, Sachse A, Kuziel WA, Maeda N, Brück W. The chemokine receptor CCR2 is involved in macrophage recruitment to the injured peripheral nervous system. J Neuroimmunol 2000;110:177–85.

[187] Silva JR, Lopes AH, Talbot J, Cecilio NT, Rossato MF, Silva RL, Souza GR, Silva CR, Lucas G, Fonseca BA, Arruda E, Alves-Filho JC, Cunha FQ, Cunha TM. Neuroimmune-Glia interactions in the sensory ganglia account for the development of acute herpetic neuralgia. J Neurosci 2017;37:6408–22.

[188] Silva CR, Melo BMS, Silva JR, Lopes AH, Pereira JA, Cecilio NT, Berlink J, Souza GG, Lucas G, Vogl T, Cunha FQ, Alves-Filho JC, Cunha TM. S100A9 plays a pivotal role in a mouse model of herpetic neuralgia via TLR4/TNF pathway. Brain Behav Immun 2020;88:353–62.

[189] Simeoli R, Montague K, Jones HR, Castaldi L, Chambers D, Kelleher JH, Vacca V, Pitcher T, Grist J, Al-Ahdal H, Wong LF, Perretti M, Lai J, Mouritzen P, Heppenstall P, Malcangio M. Exosomal cargo including microRNA regulates sensory neuron to macrophage communication after nerve trauma. Nat Commun 2017;8:1778.

[190] Solaro C, Brichetto G, Amato MP, Cocco E, Colombo B, D'Aleo G, Gasperini C, Ghezzi A, Martinelli V, Milanese C, Patti F, Trojano M, Verdun E, Mancardi GL. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. Neurology 2004;63:919–21.

[191] Sommer C, Schmidt C, George A. Hyperalgesia in experimental neuropathy is dependent on the TNF receptor 1. Exp Neurol 1998; 151:138–42.

[192] Sorge RE, LaCroix-Fralish ML, Tuttle AH, Sotocinal SG, Austin JS, Ritchie J, Chanda ML, Graham AC, Topham L, Beggs S, Salter MW, Mogil JS. Spinal cord Toll-like receptor 4 mediates inflammatory and neuropathic hypersensitivity in male but not female mice. J Neurosci 2011;31:15450–4.

[193] Starobova H, Mueller A, Allavena R, Lohman RJ, Sweet MJ, Vetter I. Minocycline prevents the development of mechanical allodynia in mouse models of vincristine-induced peripheral neuropathy. Front Neurosci 2019;13:653.

[194] Sterka D Jr, Marriott I. Characterization of nucleotide-binding oligomerization domain (NOD) protein expression in primary murine microglia. J Neuroimmunol 2006;179:65–75.

[195] Takeda M, Kato H, Takamiya A, Yoshida A, Kiyama H. Injury-specific expression of activating transcription factor-3 in retinal ganglion cells and its colocalized expression with phosphorylated c-Jun. Invest Ophthalmol Vis Sci 2000;41:2412–21.

[196] Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell 2010;140:805–20.

[197] 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 U S A 2005;102:5856–61.

[198] Thacker MA, Clark AK, Bishop T, Grist J, Yip PK, Moon LD, Thompson SW, Marchand F, McMahon SB. CCL2 is a mediator of microglia activation in neuropathic pain states. Eur J Pain 2009;13:263–72.

[199] Thacker MA, Clark AK, Bishop T, Grist J, Yip PK, Moon LD, Thompson SW, Marchand F, McMahon SB. CCL2 is a key mediator of microglia activation in neuropathic pain states. Eur J Pain 2009;13:263–72.

[200] Ton BH, Chen Q, Gaina G, Tucureanu C, Georgescu A, Strungaru C, Flonta ML, Sah D, Ristoiu V. Activation profile of dorsal root ganglia Iba-1 (+) macrophages varies with the type of lesion in rats. Acta Histochem 2013;115:840–50.

[201] Tong W, Wang W, Huang J, Ren N, Wu SX, Li YQ. Spinal high-mobility group box 1 contributes to mechanical allodynia in a rat model of bone cancer pain. Biochem Biophys Res Commun 2010;395:572–6.

[202] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, Cohen M, Evers S, Finnerup NB, First MB, Giamberardino MA, Kaasa S, Korwisi B, Kosek E, Lavand'homme P, Nicholas M, Perrot S, Scholz J, Schug S, Smith BH, Svensson P, Vlaeyen JWS, Wang SJ. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the International Classification of Diseases (ICD-11). PAIN 2019;160:19–27.

[203] Trevisan G, Benemei S, Materazzi S, De Logu F, De Siena G, Fusi C, Fortes Rossato M, Coppi E, Marone IM, Ferreira J, Geppetti P, Nassini R. TRPA1 mediates trigeminal neuropathic pain in mice downstream of monocytes/macrophages and oxidative stress. Brain 2016;139(pt 5): 1361–77.

[204] Tsou CL, Peters W, Si Y, Slaymaker S, Aslanian AM, Weisberg SP, Mack M, Charo IF. Critical roles for CCR2 and MCP-3 in monocyte mobilization from bone marrow and recruitment to inflammatory sites. J Clin Invest 2007;117:902–9.

[205] Tsujino H, Kondo E, Fukuoka T, Dai Y, Tokunaga A, Miki K, Yonenobu K, Ochi T, Noguchi K. Activating transcription factor 3 (ATF3) induction by axotomy in sensory and motoneurons: a novel neuronal marker of nerve injury. Mol Cell Neurosci 2000;15:170–82.

[206] Üçeyler N, Topuzoğlu T, Schiesser P, Hahnenkamp S, Sommer C. IL-4 deficiency is associated with mechanical hypersensitivity in mice. PLoS One 2011;6:e28205.

[207] Vabulas RM, Ahmad-Nejad P, Ghose S, Kirschning CJ, Issels RD, Wagner H. HSP70 as endogenous stimulus of the Toll/interleukin-1 receptor signal pathway. J Biol Chem 2002;277:15107–12.

[208] Vabulas RM, Wagner H, Schild H. Heat shock proteins as ligands of toll-like receptors. Curr Top Microbiol Immunol 2002;270:169–84.

[209] Van Steenwinckel J, Reaux-Le Goazigo A, Pommier B, Mauborgne A, Dansereau MA, Kitabgi P, Sarret P, Pohl M, Mélik Parsadaniantz S. CCL2 released from neuronal synaptic vesicles in the spinal cord is a major mediator of local inflammation and pain after peripheral nerve injury. J Neurosci 2011;31:5865–75.

[210] Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. Annu Rev Immunol 2015;33:643–75.

[211] Vega-Avelaira D, Géranton SM, Fitzgerald M. Differential regulation of immune responses and macrophage/neuron interactions in the dorsal root ganglion in young and adult rats following nerve injury. Mol Pain 2009;5:70.

[212] Vera G, Cabezos PA, Martín MI, Abalo R. Characterization of cannabinoid-induced relief of neuropathic pain in a rat model of cisplatin-induced neuropathy. Pharmacol Biochem Behav 2013;105: 205–12.

[213] Verge GM, Milligan ED, Maier SF, Watkins LR, Naeve GS, Foster AC. Fractalkine (CX3CL1) and fractalkine receptor (CX3CR1) distribution in spinal cord and dorsal root ganglia under basal and neuropathic pain conditions. Eur J Neurosci 2004;20:1150–60.

[214] Visser L, Jan de Heer H, Boven LA, van Riel D, van Meurs M, Melief MJ, Zähringer U, van Strijp J, Lambrecht BN, Nieuwenhuis EE, Laman JD. Proinflammatory bacterial peptidoglycan as a cofactor for the

development of central nervous system autoimmune disease. J Immunol 2005;174:808–16.

[215] Visser L, Melief MJ, van Riel D, van Meurs M, Sick EA, Inamura S, Bajramovic JJ, Amor S, Hintzen RQ, Boven LA, 't Hart BA, Laman JD. Phagocytes containing a disease-promoting Toll-like receptor/Nod ligand are present in the brain during demyelinating disease in primates. Am J Pathol 2006;169:1671–85.

[216] Von Korff M, Scher AI, Helmick C, Carter-Pokras O, Dodick DW, Goulet J, Hamill-Ruth R, LeResche L, Porter L, Tait R, Terman G, Veasley C, Mackey S. United States national pain strategy for population Research: concepts, definitions, and pilot data. J Pain 2016;17:1068–80.

[217] Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. Neuroreport 1996;7:2897–901.

[218] Walters ET. Injury-related behavior and neuronal plasticity: an evolutionary perspective on sensitization, hyperalgesia, and analgesia. Int Rev Neurobiol 1994;36:325–427.

[219] Wang PL, Yim AKY, Kim KW, Avey D, Czepielewski RS, Colonna M, Milbrandt J, Randolph GJ. Peripheral nerve resident macrophages share tissue-specific programming and features of activated microglia. Nat Commun 2020;11:2552.

[220] Watson CJ, Khaled WT. Mammary development in the embryo and adult: a journey of morphogenesis and commitment. Development 2008;135:995–1003.

[221] Wei H, Hämäläinen MM, Saarnilehto M, Koivisto A, Pertovaara A. Attenuation of mechanical hypersensitivity by an antagonist of the TRPA1 ion channel in diabetic animals. Anesthesiology 2009;111: 147–54.

[222] White FA, Bhangoo SK, Miller RJ. Chemokines: integrators of pain and inflammation. Nat Rev Drug Discov 2005;4:834–44.

[223] White FA, Sun J, Waters SM, Ma C, Ren D, Ripsch M, Steflik J, Cortright DN, Lamotte RH, Miller RJ. Excitatory monocyte chemoattractant protein-1 signaling is up-regulated in sensory neurons after chronic compression of the dorsal root ganglion. Proc Natl Acad Sci U S A 2005; 102:14092–7.

[224] Wieseler-Frank J, Maier SF, Watkins LR. Glial activation and pathological pain. Neurochem Int 2004;45:389–95.

[225] Willemen HL, Eijkelkamp N, Garza Carbajal A, Wang H, Mack M, Zijlstra J, Heijnen CJ, Kavelaars A. Monocytes/Macrophages control resolution of transient inflammatory pain. J Pain 2014;15:496–506.

[226] Wu Z, Wang S, Wu I, Mata M, Fink DJ. Activation of TLR-4 to produce tumour necrosis factor-α in neuropathic pain caused by paclitaxel. Eur J Pain 2015;19:889–98.

[227] Wu XB, Jing PB, Zhang ZJ, Cao DL, Gao MH, Jiang BC, Gao YJ. Chemokine receptor CCR2 contributes to neuropathic pain and the associated depression via increasing NR2B-mediated currents in both D1 and D2 dopamine receptor-containing medium spiny neurons in the nucleus accumbens shell. Neuropsychopharmacology 2018;43: 2320–30.

[228] Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nature 2013;496:445–55.

[229] 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.

[230] Yan X, Maixner DW, Yadav R, Gao M, Li P, Bartlett MG, Weng HR. Paclitaxel induces acute pain via directly activating toll like receptor 4. Mol Pain 2015;11:10.

[231] Ydens E, Amann L, Asselbergh B, Scott CL, Martens L, Sichien D, Mossad O, Blank T, De Prijck S, Low D, Masuda T, Saeys Y, Timmerman V, Stumm R, Ginhoux F, Prinz M, Janssens S, Guilliams M. Profiling peripheral nerve macrophages reveals two macrophage subsets with distinct localization, transcriptome and response to injury. Nat Neurosci 2020;23:676–89.

[232] Yona S, Kim KW, Wolf Y, Varol D, Breker M, Strauss-Ayali D, Viukov S, Guilliams M, Misharin A, Hume DA, Perlman H, Malissen B, Zelzer E, Jung S. Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis [published correction appears in Immunity. 2013 May 23;38(5):1073-9]. Immunity 2013;38:79–91.

[233] Yoon H, Jang YH, Kim SJ, Lee SJ, Kim SK. Toll-like receptor 2 is dispensable for an immediate-early microglial reaction to two-photon laser-induced cortical injury in vivo. Korean J Physiol Pharmacol 2015; 19:461–5.

[234] Yowtak J, Lee KY, Kim HY, Wang J, Kim HK, Chung K, Chung JM. Reactive oxygen species contribute to neuropathic pain by reducing spinal GABA release. PAIN 2011;152:844–52.

[235] Yu X, Liu H, Hamel KA, Morvan MG, Yu S, Leff J, Guan Z, Braz JM, Basbaum AI. Dorsal root ganglion macrophages contribute to both the initiation and persistence of neuropathic pain. Nat Commun 2020;11: 264.

[236] Zelenka M, Schäfers M, Sommer C. Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. PAIN 2005; 116:257–63.

[237] Zhang J, Shi XQ, Echeverry S, Mogil JS, De Koninck Y, Rivest S. Expression of CCR2 in both resident and bone marrow-derived microglia plays a critical role in neuropathic pain. J Neurosci 2007;27: 12396–406.

[238] Zhang H, Li Y, de Carvalho-Barbosa M, Kavelaars A, Heijnen CJ, Albrecht PJ, Dougherty PM. Dorsal root ganglion infiltration by macrophages contributes to paclitaxel chemotherapy-induced peripheral neuropathy. J Pain 2016;17:775–86.

[239] Zhang ZJ, Guo JS, Li SS, Wu XB, Cao DL, Jiang BC, Jing PB, Bai XQ, Li CH, Wu ZH, Lu Y, Gao YJ. TLR8 and its endogenous ligand miR-21 contribute to neuropathic pain in murine DRG. J Exp Med 2018;215: 3019–37.

[240] Zigmond RE, Echevarria FD. Macrophage biology in the peripheral nervous system after injury. Prog Neurobiol 2019;173:102–21.