

The Role of Neuroinflammation in Complex Regional Pain Syndrome: A Comprehensive Review

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Abstract: Complex Regional Pain Syndrome (CRPS) is an excess and/or prolonged pain and inflammation condition that follows an injury to a limb. The pathogenesis of CRPS is multifaceted that remains incompletely understood. Neuroinflammation is an inflammatory response in the peripheral and central nervous systems. Dysregulated neuroinflammation plays a crucial role in the initiation and maintenance of pain and nociceptive neuronal sensitization, which may contribute to the transition from acute to chronic pain and the perpetuation of chronic pain in CRPS. The key features of neuroinflammation encompass infiltration and activation of inflammatory cells and the production of inflammatory mediators in both the central and peripheral nervous systems. This article reviews the role of neuroinflammation in the onset and progression of CRPS from six perspectives: neurogenic inflammation, neuropeptides, glial cells, immune cells, cytokines, and keratinocytes. The objective is to provide insights that can inform future research and development of therapeutic targets for CRPS.

Keywords: complex regional pain syndrome, neuroinflammation, neurogenic inflammation, glial cells, keratinocytes

Introduction

Complex regional pain syndrome (CRPS) is a type of excessive pain and inflammation syndrome that typically follows an injury (eg, trauma, fracture, surgery, or local ischemia) to a limb.¹ The persisting regional pain is often disproportionate in duration and extent to the inciting injury. Based on the presence or absence of definite peripheral nerve injury, CRPS is classified into two types: CRPS type I (without definite peripheral nerve injury, formerly known as reflex sympathetic dystrophy) and CRPS type II (with definite peripheral nerve injury, previously referred to as causalgia).^{1,2} There are diverse clinical manifestations of CRPS, encompassing refractory pain, vascular alterations, and autonomic nervous system dysfunction.^{3,4} These persistent and distressing symptoms often result in disability and remarkable economic burden to families and the society. CRPS can also significantly affect patients' mental health, social relationships, and their quality of life.^{5,6} The pathophysiological mechanism of CRPS is complex and not yet fully elucidated. Possible mechanisms include inflammatory and immune responses dysregulation, autonomic nervous system dysfunction, peripheral and central sensitization, brain sensorimotor cortex remodeling, genetic susceptibility, and psychosocial factors.⁷⁻⁹

Inflammation is a biological response to tissue damage, involving the recruitment of immune cells and the release of inflammatory mediators. When this process occurs in either the peripheral or central nervous system, it is referred to as neuroinflammation.¹⁰ Similar to inflammation, neuroinflammation is characterized by the infiltration of immune cells, activation of glial cells, and increased production of inflammatory mediators in the peripheral (PNS) and central nervous system (CNS).¹⁰⁻¹² Neuroinflammation is typically a tightly regulated physiological process that facilitates the regeneration and healing of damaged tissue. However, if the regression of neuroinflammation is impeded, sustained neuroinflammation will decrease the threshold of nociceptors, leading to their activation by subthreshold stimuli.¹³⁻¹⁵ Aberrant neuroinflammation in the PNS and CNS plays a crucial role not only in the development but also in the maintenance of

chronic pain.^{16,17} Recent studies have provided supportive evidence for the role of neuroinflammation in CRPS, which may contribute to both the transition from acute to chronic pain and the persistence of chronic pain.^{8,18–20} The primary cells involved in this process include nociceptors, neurons, glial cells (such as Schwann cells, astrocytes, microglia, and oligodendrocytes), immune cells (including T cells, macrophages, and mast cells), keratinocytes and others.¹⁵

Neuroinflammation is a form of localized inflammation that surpasses systemic inflammation in its ability to initiate and sustain CRPS pain. Targeting neuroinflammation could be a potential therapeutic approach for CRPS. However, a comprehensive review summarizing the involvement of neuroinflammation in CRPS is currently lacking. Drugs developed specifically targeting neuroinflammation for the treatment of CRPS are still limited. This article reviews the role of neuroinflammation in the onset and progression of CRPS from six perspectives: neurogenic inflammation, neuropeptides, glial cell activation, immune cell infiltration, cytokines, and keratinocytes. The aim is to offer valuable insights for future research and facilitate the development of effective therapeutic targets for CRPS.

Neurogenic Inflammation

Neurogenic inflammation refers to the inflammatory response in the nervous system that is triggered by neuronal activity.^{12,21,22} Neurogenic inflammation is first observed in the skin, where mechanical or chemical stimulation can activate nociceptive receptors (particularly C fibers) within the affected tissue. This activation stimulates peripheral nerve endings, thereby facilitating the release of neuropeptides.²³ These neuropeptides interact with immunomodulatory cells, leading to the secretion of proinflammatory cytokines, local vasodilation, protein extravasation, and other inflammatory reactions.^{24,25} They also promote pain signaling and induce peripheral sensitization.^{25–28} Neuropeptides can bind to their corresponding receptors in the CNS, activating microglia and astrocytes, which in turn can amplify neurogenic inflammation.^{28–30}

Activation of C nociceptors in the periphery leads to the transmission of pain signals to the nociceptive neurons in dorsal root ganglion (DRG). Inflammatory mediators are expressed and released by nociceptive neurons through their central terminals into the spinal cord, where they persist and cause associated symptoms.^{11,25,31} These mediators include neuropeptides, glutamate, brain-derived growth factors, cytokines, chemokines, growth factors, adenosine triphosphate (ATP), and enzymes. Neurogenic inflammation serves as the primary trigger mechanism in the pathogenesis of CRPS and has been considered central in the development of CRPS^{25,32} (Figure 1).

Neuropeptide

Neuropeptides are synthesized primarily by sensory neurons in the trigeminal ganglion and DRG and then transported via axoplasmic transport to both central and peripheral nerve endings. These neuropeptides are important in signal transduction, acting on adjacent neurons to induce neurogenic inflammation as well as peripheral sensitization of CRPS.^{25,33} Both clinical trials and animal studies have demonstrated that certain neuropeptides, particularly substance P (SP), calcitonin gene-related peptide (CGRP), and neurokinin A (NKA), can be released by peripheral nerve fibers in individuals with CRPS.^{21,34–36} Dysfunction of neuropeptide-containing primary afferent C fibers leads to vascular symptoms, trophic changes, and the formation of pain in CRPS.^{36–38} The quantity of Langerhans cells is elevated in CRPS murine models and the skin of CRPS patients, while these increments are diminished in neuropeptide signaling-deficient animals.³⁹ SP and NKA can also activate NKA1 receptors, leading to local vasodilation, increased vascular permeability, and plasma extravasation.²¹ By acting on vascular smooth muscle and endothelial cells, CGRP can cause vasodilation, elevation of skin temperature, and erythema.²¹ CGRP can also enhance sweat gland activity, promote increased sweat secretion,⁴⁰ and stimulate hair growth,⁴¹ all of which are common manifestations of CRPS. In the tibial fracture model for CRPS type I, there was an increase in the expression levels of CGRP and SP in DRG at L4 and L5 levels on the affected side.³⁶ SP and CGRP have a direct effect on attracting and activating cell types involved in both innate immunity (mast cells, dendritic cells) and adaptive immunity (T lymphocytes).²¹ In the chronic constriction of sciatic nerve model of CRPS, neutral endopeptidase (NEP, a neuropeptide-degrading enzyme) gene knockout mouse were more sensitive to heat, cold, and mechanical stimuli than wild type mice. These phenotypes were only seen in animals with nerve but not tissue injuries, further validating the pivotal role of substance P and CGRP in neurogenic inflammation.⁴² In CRPS type II animal models, the expression of SP and CGRP was significantly upregulated not only

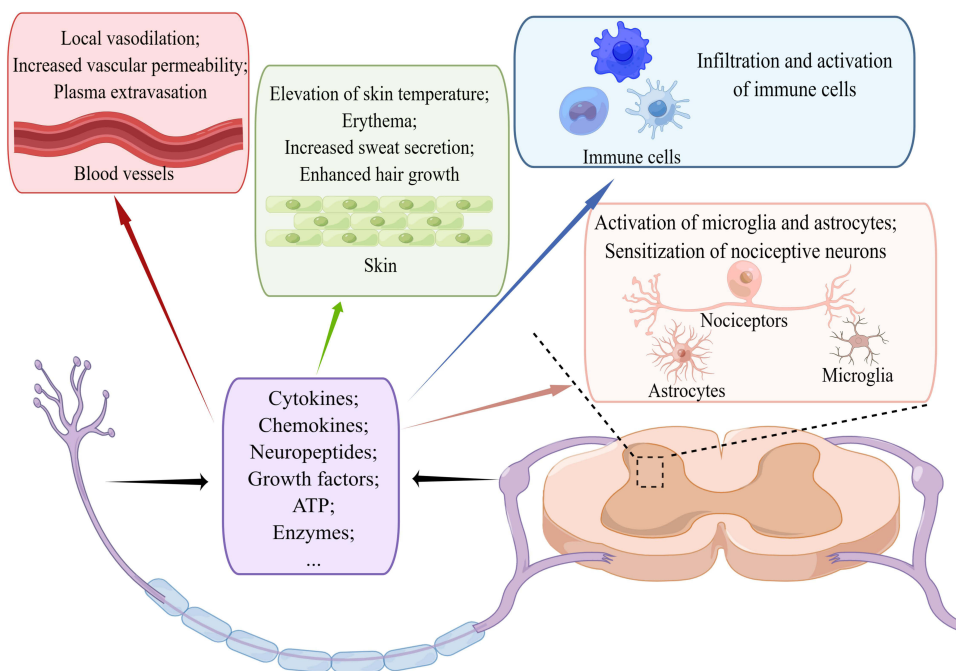


Figure 1 The role of neurogenic inflammation in the pathophysiology of CRPS. Nociceptive receptors can be activated by mechanical or chemical stimulation, leading to the release of cytokines, chemokines, neuropeptides, growth factors, ATP and enzymes. In the peripheral nervous system, these substances can induce local vasodilation, increase vascular permeability and plasma extravasation, elevate skin temperature and cause erythema, enhance sweat secretion and hair growth, as well as infiltrate and activate immune cells; in the central nervous system, they are capable of sensitizing nociceptive neurons while activating microglia and astrocytes. (By Figdraw).

Abbreviations: CRPS, complex regional pain syndrome; ATP, adenosine triphosphate.

at the injury site but also in adjacent neuromuscular tissues, indicating the involvement of neuropeptides in inflammation propagation.⁴³ On the other hand, a CRPS mouse model with substance P and CGRP receptor knockout did not exhibit abnormal pain, edema, or skin temperature elevation in the affected limb.⁴⁴ Animal studies also showed that substance P receptor antagonists alleviated skin temperature changes, edema, and pain in CRPS.⁴⁵ Angiotensin-converting enzyme inhibitors are involved in the metabolism of substance P and bradykinin, which may limit the expansion of neuroinflammatory response in these patients.⁴⁶ Additionally, recent clinical studies suggest that impaired peptide metabolism could contribute to post-traumatic pain in individuals with CRPS or limb trauma.⁴⁷

In summary, neuropeptides, particularly SP and CGRP, mediate the enhanced neurogenic inflammation and pain in CRPS^{28–30} (Figure 1). The development of pharmaceuticals targeting the inhibition of SP or CGRP signaling pathways may represent a promising approach for alleviating CRPS-associated pain.

Cytokines

Nociceptive peripheral nerve terminals are equipped with receptors and ion channels that can detect molecular mediators released during inflammation. Upon activation, nociceptive action potentials propagate to the cell bodies of nociceptors located in the DRG, which then transmit these signals to the spinal cord and brain for pain processing. After peripheral nerve injury, a range of cytokines is upregulated,⁴⁸ which can activate and sensitize C fibers,²⁹ thereby exacerbating neurogenic inflammation. Those inflammatory cytokines play a crucial role in modulating nociceptor activity and pain sensitization.⁴⁹ This part provides an overview of their involvement in neuroinflammation and CRPS.

Clinical studies have demonstrated that the equilibrium between proinflammatory and anti-inflammatory cytokines is disrupted in CRPS,⁵⁰ resulting in a shift towards a proinflammatory cytokine profile.⁵¹ The concentrations of proinflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor (TNF)- α are elevated in the serum, cerebrospinal fluid, and skin blister fluid of patients with CRPS,^{51–53} while levels of anti-inflammatory cytokines such as interleukin-4 (IL-4), interleukin-10 (IL-10) and transforming growth factor- β are reduced in their

serum.^{50,52,54,55} The elevated levels of TNF- α and IL-6 in the skin of CRPS patients persist throughout both acute and chronic stages, indicating a persistent role for cytokines in exacerbating neurogenic inflammation of CRPS.⁵⁶

Animal studies have yielded similar findings, as demonstrated by a significant upregulation of proinflammatory mediators and chemokines in the plantar, spinal dorsal horn (SDH), and DRG of rats in the chronic post-ischemia pain (CPIP) model of CRPS.^{57–59} Furthermore, upregulation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome expression has been observed in the spinal dorsal horn of rats with CPIP. Inflammasomes play a crucial role in the occurrence and development of cytokine-mediated chronic pain, with proinflammatory cytokines IL-1 β and IL-18 being the primary products of neutrophilic alkaline phosphatase (NALP) 1 and NLRP3 inflammasomes.^{19,60–62} Transcriptome analyses have demonstrated a marked increase in immune and inflammatory responses within the SDH of CPIP rats.⁶³ This activation may activate astrocytes and microglia within the SDH, ultimately resulting in the onset of mechanical allodynia.^{64,65}

During neuroinflammation, proinflammatory cytokines continuously act on their corresponding receptors on nociceptive neurons to initiate signaling cascades that alter the gating properties of ion channels through phosphorylation or other mechanisms. This ultimately leads to a decrease in firing thresholds and results in heightened pain sensitivity or “hyperalgesia”.^{13,66} Cytokines can also participate in neuropeptide transduction pathways, thereby promoting neuroinflammation and contributing to the development of CRPS. In the tibial fracture model of CRPS type I, the upregulation of TNF- α , IL-6, and C-C motif ligand (CCL) 2 expression in the spinal cord was not observed in SP and CGRP receptor knockout mice, indicating that these cytokines may serve as downstream effectors of neuropeptides during neurogenic inflammation and act as a link between peripheral and central sensitization.⁶⁷ Animal experiments have shown that the impact of SP on CRPS type I is achieved through the activation of NALP1 inflammasome and subsequent induction of IL-1 β expression.^{42,60} This pathway was more prominently activated in immobilized mice, with elevated expression levels of neurokinin-1 (NK-1) receptors, TNF- α , IL-1 β , and nerve growth factor (NGF) observed in both acute and chronic phases. These findings may explain why immobilization serves as a risk factor for CRPS.^{68,69} In a mouse model of CRPS type I, the use of neutralizing antibodies to block IL-1 β prevented activation of glial cells in the SDH and reduced pain responses, revealing that IL-1 β plays a crucial role in the pathogenesis of CRPS type I.⁷⁰

In sum, multiple pro-inflammatory cytokines play important roles in neuroinflammation and pain in CRPS (Figure 2). Blocking their signaling showed analgesic effect in rodents. However, a randomized controlled clinical trial evaluating

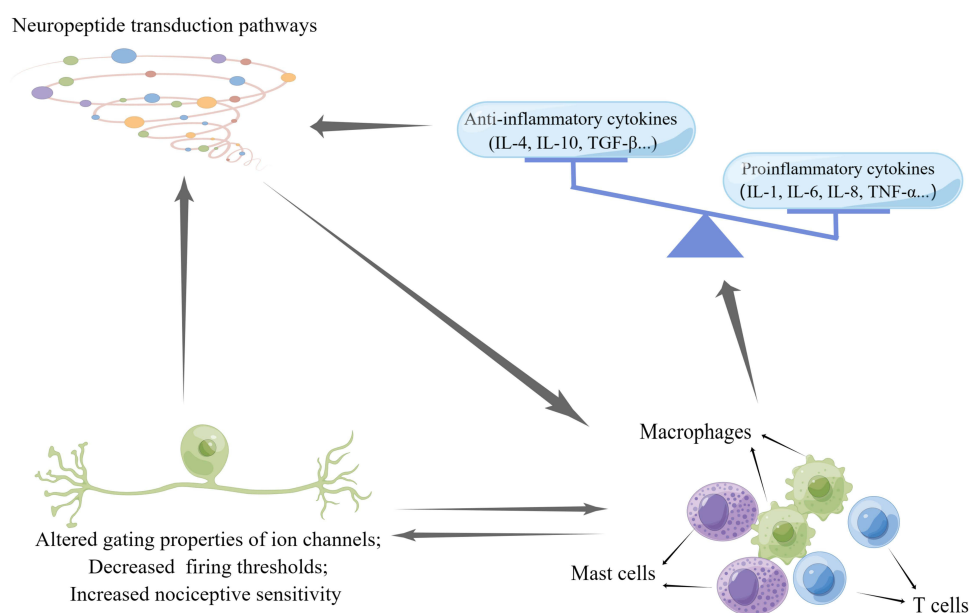


Figure 2 The role of cytokines and immune cells in the development of neuroinflammation in CRPS. Nociceptors release neuropeptides and neurotransmitters from their peripheral terminals, which activate immune responses. Immune cells infiltrate and produce numerous molecules that bind to receptors in nociceptors, leading to a shift towards a proinflammatory cytokine profile, ultimately resulting in an increase in neuronal excitability and sensitization. The bidirectional regulation and interaction between immune cells and neurons endow them with a crucial role in the pathogenesis of CRPS. (By Figdraw).

Abbreviations: CRPS, complex regional pain syndrome; IL-4, interleukin-4; IL-10, interleukin-10; IL-1, interleukin-1; IL-6, interleukin-6; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α .

the efficacy of anti-TNF- α monoclonal antibodies in treating CRPS ultimately proved to be unsuccessful. Instead of alleviating symptoms as expected, intravenous administration of TNF- α monoclonal antibody resulted in a deterioration of patients' overall health.⁷¹ Therefore, further efforts and investigations are imperative to explore the potential of cytokine-targeting drugs as a treatment for CRPS.

Immune Cells

The interaction between immune cells and neurons plays a crucial role in the development of neurogenic inflammation in CRPS.¹³ Upon activation by noxious or innocuous stimuli, nociceptors release neuropeptides and neurotransmitters from their peripheral terminals, which exert potent effects on the function of both innate and adaptive immune cells (such as macrophages, mast cells, and T lymphocytes). Receptors for neuronal mediators are expressed by these immune cells, allowing for a direct response to nociceptors.⁷² During CRPS, immune cells infiltrate and produce numerous molecules that bind to receptors in nociceptors, resulting in an increase in neuronal excitability and the formation of sensitization.^{13,73} The bidirectional regulation and interaction between immune cells and neurons endow them with a crucial role in the pathogenesis of CRPS.

Mast cells are situated close to sensory neurons and blood vessels. Upon activation, they release a variety of neuroactive and vasoactive substances such as bradykinin, histamine, prostaglandins, TNF, vascular endothelial growth factor, and serotonin via degranulation. These substances sensitize nearby nociceptive terminals and contribute to the further expansion of neuroinflammation in the affected area.²⁹ Mast cells are involved in the neuroinflammatory process of CRPS and contribute to central sensitization during its chronic phase.^{74,75} During CRPS, the release of substance P from nerve terminals may play a crucial role in mast cell degranulation and subsequent inflammatory mediator release, which can further upregulate SP expression in peptidergic nerves.⁷⁶ Skin biopsies of patients with acute CRPS revealed a significant increase in the proliferation and activation of mast cells.²⁸ In addition to contributing to pain during acute inflammation, mast cells also accumulate in chronic inflammatory conditions,⁷⁷ thereby perpetuating the chronicity of pain in CRPS.⁷⁸ Studies have shown that the loss of dermal nerve fibers in CRPS patients may hinder mast cell migration towards surviving nerve fibers due to a lack of chemotactic signals. This failure of normal interaction between nerve fibers and mast cells could be one of the underlying pathophysiological mechanisms behind CRPS.⁷⁹

Macrophages and monocytes exhibit a proinflammatory M1 phenotype, releasing numerous inflammatory cytokines, growth factors, and lipids. Their involvement in chronic pain and neuroinflammation has been extensively demonstrated.^{80–83} In chronic pain, neurons in DRG and SDH produce chemokines to attract macrophages and monocytes to infiltrate around them,^{84,85} which subsequently triggers CGRP production within these neurons.^{86,87} CPIP is a widely used method for modeling CRPS in rodents, and CPIP mice lacking macrophages did not exhibit mechanical or cold allodynia.⁸⁸

T cells are distinguished by their surface molecule and can be broadly classified into helper T (Th) cells, regulatory T (Treg) cells, and cytotoxic T cells.⁸⁹ Depending on their subtypes, Th cells can secrete either proinflammatory cytokines such as IL-1 β , TNF- α , and IL-17 or anti-inflammatory cytokines like IL-4 and IL-10.⁸⁹ The increase of CD4⁺ and CD8⁺ T cells in CRPS patients suggests an enhanced antigen-specific T lymphocyte response.^{90–92} Furthermore, research has demonstrated heightened T cell activity among individuals with CRPS. Compared to normal controls, CRPS patients exhibit an altered T cell system (Th17, Tregs, and CD39⁺ T cells), characterized by a reduced number of proinflammatory Th17 cells, an increased proportion of CD39⁺ Tregs, and minimal changes in systemic cytokine levels. These findings suggest that an increase in CD39⁺ Tregs mediates the decrease in Th17 cells observed in CRPS. This transfer of anti-inflammatory T cells may represent the mechanism underlying inflammation control in CRPS.⁹³ Additionally, the downregulation of IL-37 and tryptophan, coupled with the upregulation of Tregs, CD8⁺ T cells, and granulocyte macrophage-colony stimulating factors, may significantly promote inflammatory activation among patients diagnosed with CRPS.⁹¹

In summary, immune cells are crucial components in the pathogenesis of neuroinflammation. They are subject to regulation by neurons and can reciprocally modulate neuronal activity by releasing immunomodulatory factors, thereby significantly contributing to the development of CRPS (Figure 2).

Glial Cells

Glial cells are widely distributed throughout the nervous system, where they interact with neurons, immune cells, and blood vessels to play a crucial role in the development of neuroinflammation.^{94–96} They express a range of receptors for neuropeptides and neurotransmitters, which can be activated by the products of neurogenic inflammation. This activation triggers the release of glial mediators that regulate pain sensitivity,⁹⁷ resulting in the hypersensitivity of pain-related receptors or ion channels on neurons, ultimately leading to peripheral and central nociceptive sensitization.^{73,98,99} Glial cells have been identified as a major contributor to central nociceptive sensitization and are believed to be involved in the pathogenesis of CRPS in the chronic phase.^{100–103} Activation of astrocytes and microglia in the spinal dorsal horn of CIP rats leads to the production of various proinflammatory mediators, such as cytokines and chemokines that regulate pain processing.^{59,104–106} Among the cells in the central nervous system, microglia are the initial responders to peripheral nerve injury within a few days (pain initiation), followed by astrocytes activation within days to weeks (pain maintenance).^{107–109}

Autopsies of patients with long-term CRPS have revealed that activation of microglia and astrocytes was predominantly at the level of initial injury but extended throughout the spinal cord.¹¹⁰ Animal experiments have demonstrated that SP activated microglia and astrocytes in the spinal dorsal horn, leading to sustained central sensitization. This finding suggested a potential link between peripheral neurogenic inflammation and central sensitization.¹⁰⁰ The involvement of microglia and astrocyte interaction in CRPS has also been demonstrated in animal studies.^{104,106} Microglia are innate immune cells in the spinal cord and brain that function as sentinels of neuronal activity. They can monitor and influence neuronal activity by producing TNF- α , IL-1 β , and prostaglandin (PG) E₂, as well as neurotrophins which sensitize primary nociceptive neurons and secondary pain-mediated interneurons.^{97,111} Single-cell sequencing analysis showed that microglia produced most of the TNF- α in the spinal cord.¹¹² The previous classification of activated microglia into two phenotypes (M1 pro-inflammatory microglia and M2 anti-inflammatory microglia) was based on the presence of specific cell surface molecules and the expression of particular sets of cytokines.¹¹³ However, it is now evident that this oversimplified perspective fails to adequately capture the intricate physiology of microglial cells.¹¹⁴ Neuropeptides and neurotransmitters can trigger the transformation of microglia in the ipsilateral spinal dorsal horn from a quiescent state to an “activated” phenotype characterized by proliferation, high motility, phagocytosis, expression of novel receptors (such as P2X₄ ligand-gated ion channel), and release of proinflammatory mediators.^{115–117} This process facilitates the onset and progression of pain.⁶¹ Activation of transient receptor potential ion-channel subfamily V member 4 (TRPV4) ion channels promotes spinal microglia proliferation and activation, enhances spinal neuron excitability and plasticity, and mediates neuropathic pain.¹¹⁸

Astrocytes constitute 20% to 40% of glial cells and are non-neuronal and non-immune in nature. They execute a diverse array of physiological functions, including the maintenance of blood-brain barrier integrity, facilitation of neuroprotection and repair, as well as regulation of synaptic transmission based on their phenotype.⁹⁴ In chronic pain, astrocytes facilitate the transmission of pain signals at the spinal cord by modulating microglial activation and neuronal synaptic transmission. Moreover, astrocytes in the superior central nervous system participate in regulating chronic pain-related aversion and anxiety through mechanisms such as synapse formation regulation.¹¹⁹ Astrocytes can establish gap junctions with neurons, thereby modulating neuronal activity directly. Following peripheral nerve injury in animals, astrocytes are activated by glutamate, ATP, and cytokines (TNF- α , IL-1 β , and IL-6) that are released by afferent neurons or microglia.¹²⁰ Reactive astrocytes can be categorized into two subtypes: toxic A1 astrocytes and neuroprotective A2 astrocytes.¹²¹ A1 astrocytes induce rapid neuronal and oligodendroglia death, while A2 astrocytes exert neuroprotective effects.^{122,123} Similar to microglia, recent studies have revealed that microglia can exhibit more than two states, and the current nomenclature of A1/A2 is being refined. This classification should be considered as a continuum rather than two distinct populations.^{121,124} Activated astrocytes secrete proinflammatory cytokines and chemokines, which increase the hypersensitivity of secondary neurons in the spinal cord,¹²⁵ thereby promoting the development of neuropathic pain.^{126–128} Astrocytes can also contribute to neuronal plasticity by generating new synapses and restructuring circuits.⁹⁴ The activation of astrocytes is thought to occur after microglial activation, but it has a longer duration and therefore plays a crucial role in the persistence of chronic pain.^{94,129} Manipulation of astrocyte activity through optogenetic or chemogenetic methods can effectively regulate chronic pain.¹¹⁹

The activation of matrix metalloproteinase-2 (MMP-2)/ c-jun N-terminal kinase 1/2 (JNK-1/2) in astrocytes also contributes to the development of CRPS.¹³⁰

During the neuroinflammatory process in CRPS, neuropeptides and neurotransmitters generated by neurogenic inflammation can activate microglia and astrocytes, leading to a cascade of glial mediators that sensitize neurons and impact synaptic plasticity. This establishes a cyclic dialogue between microglia, astrocytes, and neurons that sustains central nociceptive sensitization and neuroinflammation. However, the current understanding of the underlying mechanisms involving glia and CRPS remains limited. Therefore, further in-depth investigations are warranted for comprehensive exploration.

Keratinocytes

The skin, which consists of the epidermis and dermis, is the largest organ in the human body. Keratinocytes are the primary component of the epidermal layer. In addition to their supportive and protective functions, recent studies have emphasized the significance of keratinocytes in pain development and peripheral sensitization.^{131,132} Keratinocytes have been shown to perceive a wide range of stimuli, including cold, heat, noxious, and innocuous tactile stimuli.^{133,134} When exposed to mechanical stimulation, keratinocytes transmit signals to sensory nerve terminals and release ATP, thereby activating P2X4 channels on sensory neurons, resulting in the occurrence of pain.¹³⁵ In vitro co-culture of keratinocytes and sensory neurons revealed that synapse-like structures formed between keratinocytes and pain-mediated A δ and C fibers could activate primary sensory neurons, which is dependent on the release of presynaptic vesicles from keratinocytes.¹³⁶

Skin is an organ of the neuroendocrine-immune system that has a close relationship with the nervous system. There are ample free nerve endings in the skin to detect external noxious stimuli. Neurogenic inflammation may start in the skin which is a common site of injury.²³ Keratinocytes are crucial in initiating and sustaining neuroinflammation as they are the first point of contact for external stimuli or insults. Keratinocytes, originating from the ectoderm, can secrete various neuropeptides. A significant proliferation of keratinocytes has been observed in the skin of patients with CRPS. Besides being secreted in the serum, CGRP is highly expressed in the keratinocytes of CRPS patients and can stimulate the proliferation and cytokine secretion of keratinocytes.¹³⁷ When substance P and CGRP were injected into the plantar of mice, nociceptive stimuli mediated secretion of IL-1 β by keratinocytes was increased. However, administering an IL-1 receptor antagonist effectively relieved pain induced by these neuropeptides.⁶² In CIPR rats, activation of N-methyl-d-aspartate receptors (NMDA) in keratinocytes triggers the release of inflammatory factors, leading to the activation of astrocytes and microglia in the spinal cord and resulting in both peripheral and central sensitization⁵⁹ (Figure 3).

After converting noxious stimuli into electrical signals, sensory nerve fibers must transmit them to the cell bodies of sensory neurons located in the DRG. Pain perception, transduction, and transmission can be regulated by pain-regulatory substances such as neuropeptides and cytokines secreted by keratinocytes. Keratinocytes serve as a significant origin of inflammatory mediators associated with pain. Studies have demonstrated that keratinocytes undergo proliferation and activation in a fracture model of CRPS, resulting in the secretion of cytokines such as IL-1 β , IL-6, and TNF- α , which subsequently promote the development of hyperalgesia.¹³⁸ In addition, keratinocytes are capable of releasing opioid peptides such as β -endorphin and proenkephalin to modulate the occurrence and progression of pain.¹³⁹

Conclusions

Neuroinflammation is essential in the initiation and perpetuation of CRPS, involving intricate mechanisms that encompass multiple links in the pain transduction pathway from peripheral nociceptors to the central nervous system. These processes include nociceptive perception, transduction, transmission, and modulation. This article presents a comprehensive overview of the underlying mechanisms of neuroinflammation in CRPS, with a particular focus on neurogenic inflammation, inflammatory mediators (peptides and cytokines), immune cells, glial cells, and keratinocytes. Researches on pharmaceutical interventions targeting the neuroinflammatory mechanism underlying CRPS are currently insufficient. Further investigation into the regulatory mechanisms governing various components of neuroinflammation is

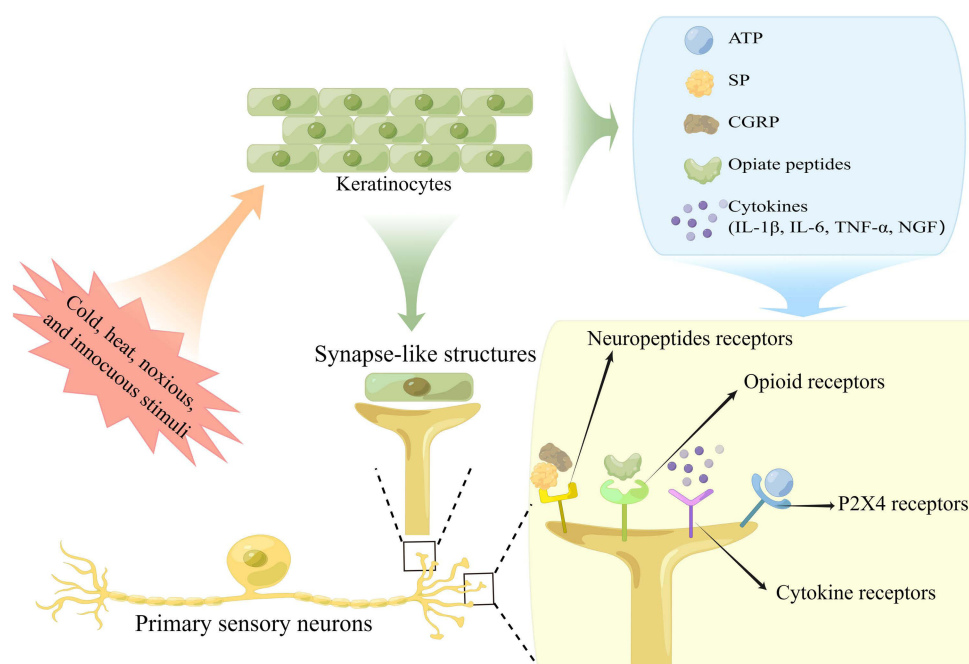


Figure 3 The role of keratinocytes in the development of neuroinflammation in CRPS. When exposed to various stimuli, such as cold, heat, and noxious and innocuous stimulation, keratinocytes can release ATP, SP, CGRP, IL-1 β , IL-6, TNF- α and NGF to activate sensory nociceptors. Additionally, keratinocytes are capable of forming synapse-like structures to sensitize peripheral nociceptors. (By Figdraw).

Abbreviations: CRPS, complex regional pain syndrome; ATP, adenosine-triphosphate; SP, substance P; CGRP, calcitonin gene-related peptide; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; TNF- α , tumor necrosis factor-alpha; NGF, nerve growth factor; P2X4, purinergic P2X4 receptors.

imperative to identify potential therapeutic targets that offer high efficacy and minimal adverse effects. Gaining a comprehensive understanding of the unique and individual roles that each component plays in the process of neuroinflammation may facilitate the discovery of novel insights and the development of innovative approaches to combat this debilitating condition. However, this review only provides a macroscopic overview of the role of neuroinflammation in CRPS, without delving into subcellular processes such as intricate signaling cascades, ion channels, oxidative injury, and mitochondrial autophagy. Furthermore, the review neglects to mention therapeutic approaches targeting neuroinflammation in CRPS.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160(1):28–37. doi:10.1097/j.pain.0000000000001390
- Harden RN, McCabe CS, Goebel A, et al. Complex regional pain syndrome: practical diagnostic and treatment guidelines. *Pain Med*. 2022;23(Suppl 1):S1–s53. doi:10.1093/pm/pnac046
- David Clark J, Tawfik VL, Tajerian M, Kingery WS. Autoinflammatory and autoimmune contributions to complex regional pain syndrome. *Mol Pain*. 2018;14:1744806918799127. doi:10.1177/1744806918799127
- Birklein F, Ajit SK, Goebel A, Perez R, Sommer C. Complex regional pain syndrome - phenotypic characteristics and potential biomarkers. *Nat Rev Neurol*. 2018;14(5):272–284. doi:10.1038/nrneurol.2018.20
- Elsamadicy AA, Yang S, Sergesketter AR, et al. Prevalence and cost analysis of complex regional pain syndrome (CRPS): a role for neuromodulation. *Neuromodulation*. 2018;21(5):423–430. doi:10.1111/ner.12691

6. Ayyaswamy B, Saeed B, Anand A, Chan L, Shetty V. Quality of life after amputation in patients with advanced complex regional pain syndrome: a systematic review. *EFORT Open Rev.* 2019;4(9):533–540. doi:10.1302/2058-5241.4.190008
7. Kessler A, Yoo M, Calisoff R. Complex regional pain syndrome: an updated comprehensive review. *NeuroRehabilitation.* 2020;47(3):253–264. doi:10.3233/nre-208001
8. Shim H, Rose J, Halle S, Shekane P. Complex regional pain syndrome: a narrative review for the practising clinician. *Br J Anaesth.* 2019;123(2):e424–e433. doi:10.1016/j.bja.2019.03.030
9. Baronio M, Sadia H, Paolacci S, et al. Molecular aspects of regional pain syndrome. *Pain Res Manag.* 2020;2020:7697214. doi:10.1155/2020/7697214
10. Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. *Nat Rev Drug Discov.* 2014;13(7):533–548. doi:10.1038/nrd4334
11. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth.* 2019;33(1):131–139. doi:10.1007/s00540-018-2579-4
12. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology.* 2018;129(2):343–366. doi:10.1097/aln.0000000000002130
13. Pinho-Ribeiro FA, Verri WA, Chiu IM. Nociceptor sensory neuron–immune interactions in pain and inflammation. *Trends Immunol.* 2017;38(1):5–19. doi:10.1016/j.it.2016.10.001
14. Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. *Br J Anaesth.* 2013;111(1):26–37. doi:10.1093/bja/aet128
15. Huh Y, Ji RR, Chen G. Neuroinflammation, bone marrow stem cells, and chronic pain. *Front Immunol.* 2017;8:1014. doi:10.3389/fimmu.2017.01014
16. Gao YJ, Ji RR. Chemokines, neuronal–glial interactions, and central processing of neuropathic pain. *Pharmacol Ther.* 2010;126(1):56–68. doi:10.1016/j.pharmthera.2010.01.002
17. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. *J Neurosci.* 2008;28(20):5189–5194. doi:10.1523/jneurosci.3338-07.2008
18. Seo S, Jung YH, Lee D, et al. Abnormal neuroinflammation in fibromyalgia and CRPS using [11C]-(R)-PK11195 PET. *PLoS One.* 2021;16(2):e0246152. doi:10.1371/journal.pone.0246152
19. Zhang Y, Chen R, Hu Q, et al. Electroacupuncture ameliorates mechanical allodynia of a rat model of CRPS-I via Suppressing NLRP3 inflammasome activation in spinal cord dorsal horn neurons. *Front Cell Neurosci.* 2022;16:826777. doi:10.3389/fncel.2022.826777
20. Jung YH, Kim H, Jeon SY, et al. Brain metabolites and peripheral biomarkers associated with neuroinflammation in complex regional pain syndrome using [11C]-(R)-PK11195 positron emission tomography and magnetic resonance spectroscopy: a pilot study. *Pain Med.* 2019;20(3):504–514. doi:10.1093/pm/pny111
21. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci.* 2012;15(8):1063–1067. doi:10.1038/nn.3144
22. Xanthos DN, Sandkühler J. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. *Nat Rev Neurosci.* 2014;15(1):43–53. doi:10.1038/nrn3617
23. Torii H, Hosoi J, Beissert S, et al. Regulation of cytokine expression in macrophages and the Langerhans cell-like line XS52 by calcitonin gene-related peptide. *J Leukoc Biol.* 1997;61(2):216–223. doi:10.1002/jlb.61.2.216
24. Szolcsányi J. Capsaicin-sensitive sensory nerve terminals with local and systemic efferent functions: facts and scopes of an unorthodox neuroregulatory mechanism. *Prog Brain Res.* 1996;113:343–359. doi:10.1016/s0079-6123(08)61097-3
25. Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. *Nat Rev Rheumatol.* 2015;11(11):639–648. doi:10.1038/nrrheum.2015.100
26. Gonzalez HL, Carmichael N, Dostrovsky JO, Charlton MP. Evaluation of the time course of plasma extravasation in the skin by digital image analysis. *J Pain.* 2005;6(10):681–688. doi:10.1016/j.jpain.2005.06.004
- 27.Coderre TJ, Bennett GJ. A hypothesis for the cause of complex regional pain syndrome-type I (reflex sympathetic dystrophy): pain due to deep-tissue microvascular pathology. *Pain Med.* 2010;11(8):1224–1238. doi:10.1111/j.1526-4637.2010.00911.x
28. Birklein F, Drummond PD, Li W, et al. Activation of cutaneous immune responses in complex regional pain syndrome. *J Pain.* 2014;15(5):485–495. doi:10.1016/j.jpain.2014.01.490
29. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). *Neurosci Lett.* 2008;437(3):199–202. doi:10.1016/j.neulet.2008.03.081
30. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain.* 2012;13(10):936–944. doi:10.1016/j.jpain.2012.07.005
31. Holzer P. Neurogenic vasodilatation and plasma leakage in the skin. *Gen Pharmacol.* 1998;30(1):5–11. doi:10.1016/s0306-3623(97)00078-5
32. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet.* 1993;342(8878):1012–1016. doi:10.1016/0140-6736(93)92877-v
33. Shi X, Guo TZ, Li W, et al. Exercise reverses nociceptive sensitization, upregulated neuropeptide signaling, inflammatory changes, anxiety, and memory impairment in a mouse tibia fracture model. *Anesthesiology.* 2018;129(3):557–575. doi:10.1097/aln.0000000000002332
34. Weber M, Birklein F, Neundörfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. *Pain.* 2001;91(3):251–257. doi:10.1016/s0304-3959(00)00445-0
35. Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. *Neurology.* 2001;57(12):2179–2184. doi:10.1212/wnl.57.12.2179
36. Wei T, Li WW, Guo TZ, et al. Post-junctional facilitation of Substance P signaling in a tibia fracture rat model of complex regional pain syndrome type I. *Pain.* 2009;144(3):278–286. doi:10.1016/j.pain.2009.04.020
37. Bruehl S, Warner DS. An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology.* 2010;113(3):713–725. doi:10.1097/ALN.0b013e3181e3db38
38. Marinus J, Moseley GL, Birklein F, et al. Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol.* 2011;10(7):637–648. doi:10.1016/s1474-4422(11)70106-5

39. Li WW, Guo TZ, Shi X, et al. Neuropeptide regulation of adaptive immunity in the tibia fracture model of complex regional pain syndrome. *J Neuroinflammation*. 2018;15(1):105. doi:10.1186/s12974-018-1145-1
40. Schlereth T, Dittmar JO, Seewald B, Birklein F. Peripheral amplification of sweating—a role for calcitonin gene-related peptide. *J Physiol*. 2006;576(Pt 3):823–832. doi:10.1113/jphysiol.2006.116111
41. Hagner S, Haberberger RV, Overkamp D, Hoffmann R, Voigt KH, McGregor GP. Expression and distribution of calcitonin receptor-like receptor in human hairy skin. *Peptides*. 2002;23(1):109–116. doi:10.1016/s0196-9781(01)00586-1
42. Krämer HH, He L, Lu B, Birklein F, Sommer C. Increased pain and neurogenic inflammation in mice deficient of neutral endopeptidase. *Neurobiol Dis*. 2009;35(2):177–183. doi:10.1016/j.nbd.2008.11.002
43. Ota H, Arai T, Iwatsuki K, et al. Pathological mechanism of musculoskeletal manifestations associated with CRPS type II: an animal study. *Pain*. 2014;155(10):1976–1985. doi:10.1016/j.pain.2014.06.016
44. Guo TZ, Wei T, Shi X, et al. Neuropeptide deficient mice have attenuated nociceptive, vascular, and inflammatory changes in a tibia fracture model of complex regional pain syndrome. *Mol Pain*. 2012;8:85. doi:10.1186/1744-8069-8-85
45. Kingery WS, Davies MF, Clark JD. A substance P receptor (NK1) antagonist can reverse vascular and nociceptive abnormalities in a rat model of complex regional pain syndrome type II. *Pain*. 2003;104(1–2):75–84. doi:10.1016/s0304-3959(02)00467-0
46. de Mos M, Huygen F, Stricker CBH, Dieleman JP, Sturkenboom M. The association between ACE inhibitors and the complex regional pain syndrome: suggestions for a neuro-inflammatory pathogenesis of CRPS. *Pain*. 2009;142(3):218–224. doi:10.1016/j.pain.2008.12.032
47. König S, Engl C, Bayer M, et al. Substance P serum degradation in complex regional pain syndrome - another piece of the puzzle? *J Pain*. 2022;23(3):501–507. doi:10.1016/j.jpain.2021.10.005
48. Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. *Pain*. 2018;159(3):595–602. doi:10.1097/j.pain.0000000000001122
49. Verri WA, Cunha TM, Parada CA, Poole S, Cunha FQ, Ferreira SH. Hypernociceptive role of cytokines and chemokines: targets for analgesic drug development? *Pharmacol Ther*. 2006;112(1):116–138. doi:10.1016/j.pharmthera.2006.04.001
50. König S, Schlereth T, Birklein F. Molecular signature of complex regional pain syndrome (CRPS) and its analysis. *Expert Rev Proteomics*. 2017;14(10):857–867. doi:10.1080/14789450.2017.1366859
51. Üçeyler N, Eberle T, Rolke R, Birklein F, Schwartzman RJ. Differential expression patterns of cytokines in complex regional pain syndrome. *Pain*. 2007;132(1–2):195–205. doi:10.1016/j.pain.2007.07.031
52. Alexander GM, van Rijn MA, van Hilten JJ, Perreault MJ, Schwartzman RJ. Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. *Pain*. 2005;116(3):213–219. doi:10.1016/j.pain.2005.04.013
53. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Mechanical hyperalgesia in complex regional pain syndrome: a role for TNF-alpha? *Neurology*. 2005;65(2):311–313. doi:10.1212/01.wnl.0000168866.62086.8f
54. Alexander GM, Perreault MJ, Reichenberger ER, Schwartzman RJ. Changes in immune and glial markers in the CSF of patients with complex regional pain syndrome. *Brain Behav Immun*. 2007;21(5):668–676. doi:10.1016/j.bbi.2006.10.009
55. van den Berg C, de Bree PN, Huygen F, Tiemensma J. Glucocorticoid treatment in patients with complex regional pain syndrome: a systematic review. *Eur J Pain*. 2022;26(10):2009–2035. doi:10.1002/ejp.2025
56. Dirckx M, Stronks DL, van Bodegraven-Hof EA, Wesseldijk F, Groeneweg JG, Huygen FJ. Inflammation in cold complex regional pain syndrome. *Acta Anaesthesiol Scand*. 2015;59(6):733–739. doi:10.1111/aas.12465
57. Chae JS, Park H, Ahn SH, et al. The effect of super-repressor IkB-Loaded Exosomes (Exo-srIkBs) in chronic post-ischemia pain (CPIP) models. *Pharmaceutics*. 2023;15(2):553. doi:10.3390/pharmaceutics15020553
58. de Oliveira Galassi T, Fernandes PF, Salgado ASI, et al. Preventive supplementation of omega-3 reduces pain and pro-inflammatory cytokines in a mouse model of complex regional pain syndrome type I. *Front Integr Neurosci*. 2022;16:840249. doi:10.3389/fnint.2022.840249
59. Xu X, Tao X, Huang P, et al. N-methyl-D-aspartate receptor subunit 2B on keratinocyte mediates peripheral and central sensitization in chronic post-ischemic pain in male rats. *Brain Behav Immun*. 2020;87:579–590. doi:10.1016/j.bbi.2020.02.003
60. Li WW, Guo TZ, Liang D, et al. The NALP1 inflammasome controls cytokine production and nociception in a rat fracture model of complex regional pain syndrome. *Pain*. 2009;147(1–3):277–286. doi:10.1016/j.pain.2009.09.032
61. Chen R, Yin C, Fang J, Liu B. The NLRP3 inflammasome: an emerging therapeutic target for chronic pain. *J Neuroinflammation*. 2021;18(1):84. doi:10.1186/s12974-021-02131-0
62. Shi X, Wang L, Li X, Sahbaie P, Kingery WS, Clark JD. Neuropeptides contribute to peripheral nociceptive sensitization by regulating interleukin-1 β production in keratinocytes. *Anesth Analg*. 2011;113(1):175–183. doi:10.1213/ANE.0b013e31821a0258
63. Chen R, Yin C, Hu Q, et al. Expression profiling of spinal cord dorsal horn in a rat model of complex regional pain syndrome type-I uncovers potential mechanisms mediating pain and neuroinflammation responses. *J Neuroinflammation*. 2020;17(1):162. doi:10.1186/s12974-020-01834-0
64. Wei XH, Yang T, Wu Q, et al. Peri-sciatic administration of recombinant rat IL-1 β induces mechanical allodynia by activation of src-family kinases in spinal microglia in rats. *Exp Neurol*. 2012;234(2):389–397. doi:10.1016/j.expneurol.2012.01.001
65. Yan X, Li F, Maixner DW, et al. Interleukin-1 β released by microglia initiates the enhanced glutamatergic activity in the spinal dorsal horn during paclitaxel-associated acute pain syndrome. *Glia*. 2019;67(3):482–497. doi:10.1002/glia.23557
66. Wood JN, Boorman JP, Okuse K, Baker MD. Voltage-gated sodium channels and pain pathways. *J Neurobiol*. 2004;61(1):55–71. doi:10.1002/neu.20094
67. Shi X, Guo TZ, Wei T, Li WW, Clark DJ, Kingery WS. Facilitated spinal neuropeptide signaling and upregulated inflammatory mediator expression contribute to postfracture nociceptive sensitization. *Pain*. 2015;156(10):1852–1863. doi:10.1097/j.pain.0000000000000204
68. Guo TZ, Wei T, Li WW, Li XQ, Clark JD, Kingery WS. Immobilization contributes to exaggerated neuropeptide signaling, inflammatory changes, and nociceptive sensitization after fracture in rats. *J Pain*. 2014;15(10):1033–1045. doi:10.1016/j.jpain.2014.07.004
69. Wei T, Guo TZ, Li WW, Kingery WS, Clark JD. Acute versus chronic phase mechanisms in a rat model of CRPS. *J Neuroinflammation*. 2016;13:14. doi:10.1186/s12974-015-0472-8
70. Helyes Z, Tékus V, Szentes N, et al. Transfer of complex regional pain syndrome to mice via human autoantibodies is mediated by interleukin-1-induced mechanisms. *Proc Natl Acad Sci U S A*. 2019;116(26):13067–13076. doi:10.1073/pnas.1820168116
71. Dirckx M, Groeneweg G, Wesseldijk F, Stronks DL, Huygen FJ. Report of a preliminary discontinued double-blind, randomized, placebo-controlled trial of the anti-TNF- α chimeric monoclonal antibody infliximab in complex regional pain syndrome. *Pain Pract*. 2013;13(8):633–640. doi:10.1111/papr.12078

72. Andersson U, Tracey KJ. Reflex principles of immunological homeostasis. *Annu Rev Immunol*. 2012;30:313–335. doi:10.1146/annurev-immunol-020711-075015
73. R-R J, Chameassian A, Zhang Y-Q. Pain regulation by non-neuronal cells and inflammation. *Science*. 2016;354(6312):572–577. doi:10.1126/science.aaf8924
74. Dirckx M, Groeneweg G, van Daele PL, Stronks DL, Huygen FJ. Mast cells: a new target in the treatment of complex regional pain syndrome? *Pain Pract*. 2013;13(8):599–603. doi:10.1111/papr.12049
75. Huygen FJ, Ramdhani N, van Toorenenbergen A, Klein J, Zijlstra FJ. Mast cells are involved in inflammatory reactions during complex regional pain syndrome type I. *Immunol Lett*. 2004;91(2–3):147–154. doi:10.1016/j.imlet.2003.11.013
76. Schlereth T, Birklein F. Mast cells: source of inflammation in complex regional pain syndrome? *Anesthesiology*. 2012;116(4):756–757. doi:10.1097/ALN.0b013e31824bb143
77. Oliveira SM, Drewes CC, Silva CR, et al. Involvement of mast cells in a mouse model of postoperative pain. *Eur J Pharmacol*. 2011;672(1–3):88–95. doi:10.1016/j.ejphar.2011.10.001
78. Li WW, Guo TZ, Liang DY, Sun Y, Kingery WS, Clark JD. Substance P signaling controls mast cell activation, degranulation, and nociceptive sensitization in a rat fracture model of complex regional pain syndrome. *Anesthesiology*. 2012;116(4):882–895. doi:10.1097/ALN.0b013e31824bb303
79. Morellini N, Finch PM, Goebel A, Drummond PD. Dermal nerve fibre and mast cell density, and proximity of mast cells to nerve fibres in the skin of patients with complex regional pain syndrome. *Pain*. 2018;159(10):2021–2029. doi:10.1097/j.pain.0000000000001304
80. Kobayashi Y, Kiguchi N, Fukazawa Y, Saika F, Maeda T, Kishioka S. Macrophage-T cell interactions mediate neuropathic pain through the glucocorticoid-induced tumor necrosis factor ligand system. *J Biol Chem*. 2015;290(20):12603–12613. doi:10.1074/jbc.M115.636506
81. Schuh CD, Pierre S, Weigert A, et al. Prostacyclin mediates neuropathic pain through interleukin 1 β -expressing resident macrophages. *Pain*. 2014;155(3):545–555. doi:10.1016/j.pain.2013.12.006
82. Trevisan G, Benemei S, Materazzi S, et al. TRPA1 mediates trigeminal neuropathic pain in mice downstream of monocytes/macrophages and oxidative stress. *Brain*. 2016;139(Pt 5):1361–1377. doi:10.1093/brain/aww038
83. Old EA, Nadkarni S, Grist J, et al. Monocytes expressing CX3CR1 orchestrate the development of vincristine-induced pain. *J Clin Invest*. 2014;124(5):2023–2036. doi:10.1172/jci71389
84. Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. *Neurosci Bull*. 2012;28(2):131–144. doi:10.1007/s12264-012-1219-5
85. Liu XJ, Zhang Y, Liu T, et al. Nociceptive neurons regulate innate and adaptive immunity and neuropathic pain through MyD88 adapter. *Cell Res*. 2014;24(11):1374–1377. doi:10.1038/cr.2014.106
86. Massier J, Eitner A, Segond von Banchet G, Schaible HG. Effects of differently activated rodent macrophages on sensory neurons: implications for arthritis pain. *Arthritis Rheumatol*. 2015;67(8):2263–2272. doi:10.1002/art.39134
87. Segond von Banchet G, Boettger MK, Fischer N, Gajda M, Bräuer R, Schaible H-G. Experimental arthritis causes tumor necrosis factor- α -dependent infiltration of macrophages into rat dorsal root ganglia which correlates with pain-related behavior. *Pain*. 2009;145(1):151–159. doi:10.1016/j.pain.2009.06.002
88. De Logu F, Prá SD D, de David Antoniazzi CT, et al. Macrophages and Schwann cell TRPA1 mediate chronic allodynia in a mouse model of complex regional pain syndrome type I. *Brain Behav Immun*. 2020;88:535–546. doi:10.1016/j.bbi.2020.04.037
89. Palmer MT, Weaver CT. Autoimmunity: increasing suspects in the CD4+ T cell lineup. *Nat Immunol*. 2010;11(1):36–40. doi:10.1038/ni.1802
90. Russo MA, Fiore NT, van Vreden C, et al. Expansion and activation of distinct central memory T lymphocyte subsets in complex regional pain syndrome. *J Neuroinflammation*. 2019;16(1):63. doi:10.1186/s12974-019-1449-9
91. Russo MA, Georgius P, Pires AS, et al. Novel immune biomarkers in complex regional pain syndrome. *J Neuroimmunol*. 2020;347:577330. doi:10.1016/j.jneuroim.2020.577330
92. Bharwani KD, Dik WA, Dirckx M, Huygen F. Highlighting the role of biomarkers of inflammation in the diagnosis and management of complex regional pain syndrome. *Mol Diagn Ther*. 2019;23(5):615–626. doi:10.1007/s40291-019-00417-x
93. Bharwani KD, Dirckx M, Stronks DL, Dik WA, Schreurs MWJ, Huygen F. Elevated plasma levels of sIL-2R in Complex regional pain syndrome: a pathogenic role for T-lymphocytes? *Mediators Inflamm*. 2017;2017:2764261. doi:10.1155/2017/2764261
94. Ji RR, Donnelly CR, Nedergaard M. Astrocytes in chronic pain and itch. *Nat Rev Neurosci*. 2019;20(11):667–685. doi:10.1038/s41583-019-0218-1
95. Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. *Nat Rev Neurosci*. 2018;19(3):138–152. doi:10.1038/nrn.2018.2
96. Hanani M, Huang TY, Cherkas PS, Ledda M, Pannese E. Glial cell plasticity in sensory ganglia induced by nerve damage. *Neuroscience*. 2002;114(2):279–283. doi:10.1016/s0306-4522(02)00279-8
97. Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? *Pain*. 2013;154(0 1):S10–S28. doi:10.1016/j.pain.2013.06.022
98. Kiguchi N, Kobayashi D, Saika F, Matsuzaki S, Kishioka S. Pharmacological regulation of neuropathic pain driven by inflammatory macrophages. *Int J Mol Sci*. 2017;18:11.
99. Tsuda M, Inoue K. Neuron-microglia interaction by purinergic signaling in neuropathic pain following neurodegeneration. *Neuropharmacology*. 2016;104:76–81. doi:10.1016/j.neuropharm.2015.08.042
100. Li WW, Guo TZ, Shi X, et al. Substance P spinal signaling induces glial activation and nociceptive sensitization after fracture. *Neuroscience*. 2015;310:73–90. doi:10.1016/j.neuroscience.2015.09.036
101. Linnman C, Becerra L, Borsook D. Inflaming the brain: CRPS a model disease to understand neuroimmune interactions in chronic pain. *J Neuroimmune Pharmacol*. 2013;8(3):547–563. doi:10.1007/s11481-012-9422-8
102. Banati RB. Neuropathological imaging: in vivo detection of glial activation as a measure of disease and adaptive change in the brain. *Br Med Bull*. 2003;65:121–131. doi:10.1093/bmb/65.1.121
103. Banati RB, Cagnin A, Brooks DJ, et al. Long-term trans-synaptic glial responses in the human thalamus after peripheral nerve injury. *Neuroreport*. 2001;12(16):3439–3442. doi:10.1097/00001756-200111160-00012
104. Tang Y, Liu L, Xu D, et al. Interaction between astrocytic colony stimulating factor and its receptor on microglia mediates central sensitization and behavioral hypersensitivity in chronic post ischemic pain model. *Brain Behav Immun*. 2018;68:248–260. doi:10.1016/j.bbi.2017.10.023
105. Xu J, Tang Y, Xie M, et al. Activation of cannabinoid receptor 2 attenuates mechanical allodynia and neuroinflammatory responses in a chronic post-ischemic pain model of complex regional pain syndrome type I in rats. *Eur J Neurosci*. 2016;44(12):3046–3055. doi:10.1111/ejn.13414

106. Luo X, Tai WL, Sun L, et al. Crosstalk between astrocytic CXCL12 and microglial CXCR4 contributes to the development of neuropathic pain. *Mol Pain*. 2016;12:174480691663638. doi:10.1177/1744806916636385
107. Raghavendra V, Tanga F, DeLeo JA. Inhibition of microglial activation attenuates the development but not existing hypersensitivity in a rat model of neuropathy. *J Pharmacol Exp Ther*. 2003;306(2):624–630. doi:10.1124/jpet.103.052407
108. Zhang J, De Koninck Y. Spatial and temporal relationship between monocyte chemoattractant protein-1 expression and spinal glial activation following peripheral nerve injury. *J Neurochem*. 2006;97(3):772–783. doi:10.1111/j.1471-4159.2006.03746.x
109. Katsura H, Obata K, Mizushima T, et al. Activation of Src-family kinases in spinal microglia contributes to mechanical hypersensitivity after nerve injury. *J Neurosci*. 2006;26(34):8680–8690. doi:10.1523/jneurosci.1771-06.2006
110. Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. *Brain Behav Immun*. 2009;23(1):85–91. doi:10.1016/j.bbi.2008.08.004
111. Tsujikawa S, DeMeulenaere KE, Centeno MV, et al. Regulation of neuropathic pain by microglial Orai1 channels. *Sci Adv*. 2023;9(4):eade7002. doi:10.1126/sciadv.ade7002
112. Berta T, Park CK, Xu ZZ, et al. Extracellular caspase-6 drives murine inflammatory pain via microglial TNF- α secretion. *J Clin Invest*. 2014;124(3):1173–1186. doi:10.1172/jci72230
113. Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR. Microglia in pain: detrimental and protective roles in pathogenesis and resolution of pain. *Neuron*. 2018;100(6):1292–1311. doi:10.1016/j.neuron.2018.11.009
114. Butovsky O, Weiner HL. Microglial signatures and their role in health and disease. *Nat Rev Neurosci*. 2018;19(10):622–635. doi:10.1038/s41583-018-0057-5
115. Beggs S, Trang T, Salter MW. P2X4R+ microglia drive neuropathic pain. *Nat Neurosci*. 2012;15(8):1068–1073. doi:10.1038/nn.3155
116. Calvo M, Bennett DL. The mechanisms of microgliosis and pain following peripheral nerve injury. *Exp Neurol*. 2012;234(2):271–282. doi:10.1016/j.expneurol.2011.08.018
117. Zhang RX, Li A, Liu B, et al. IL-1ra alleviates inflammatory hyperalgesia through preventing phosphorylation of NMDA receptor NR-1 subunit in rats. *Pain*. 2008;135(3):232–239. doi:10.1016/j.pain.2007.05.023
118. Hu X, Du L, Liu S, et al. A TRPV4-dependent neuroimmune axis in the spinal cord promotes neuropathic pain. *J Clin Invest*. 2023;133(5). doi:10.1172/jci161507
119. Lu HJ, Gao YJ. Astrocytes in chronic pain: cellular and molecular mechanisms. *Neurosci Bull*. 2023;39(3):425–439. doi:10.1007/s12264-022-00961-3
120. Li T, Tang Z, Wei J, Zhou Z, Wang B. Unambiguous tracking technique based on combined correlation functions for sine BOC signals. *J Navigation*. 2019;72(1):140–154. doi:10.1017/S0373463318000498
121. Escartin C, Garea E, Lakatos A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci*. 2021;24(3):312–325. doi:10.1038/s41593-020-00783-4
122. Miller SJ. Astrocyte heterogeneity in the adult central nervous system. *Front Cell Neurosci*. 2018;12:401. doi:10.3389/fncel.2018.00401
123. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481–487. doi:10.1038/nature21029
124. Zhu A, Cui H, Su W, Liu C, Yu X, Huang Y. C3aR in astrocytes mediates post-thoracotomy pain by inducing A1 astrocytes in male rats. *Biochim Biophys Acta Mol Basis Dis*. 2023;1869(5):166672. doi:10.1016/j.bbdis.2023.166672
125. Gao Y-J, R-R J. Targeting astrocyte signaling for chronic pain. *Neurotherapeutics*. 2010;7(4):482–493. doi:10.1016/j.nurt.2010.05.016
126. Imai S, Ikegami D, Yamashita A, et al. Epigenetic transcriptional activation of monocyte chemotactic protein 3 contributes to long-lasting neuropathic pain. *Brain*. 2013;136(Pt 3):828–843. doi:10.1093/brain/aw330
127. Gao YJ, Zhang L, Samad OA, et al. JNK-induced MCP-1 production in spinal cord astrocytes contributes to central sensitization and neuropathic pain. *J Neurosci*. 2009;29(13):4096–4108. doi:10.1523/jneurosci.3623-08.2009
128. Zhang ZJ, Cao DL, Zhang X, Ji RR, Gao YJ. Chemokine contribution to neuropathic pain: respective induction of CXCL1 and CXCR2 in spinal cord astrocytes and neurons. *Pain*. 2013;154(10):2185–2197. doi:10.1016/j.pain.2013.07.002
129. Cheng T, Xu Z, Ma X. The role of astrocytes in neuropathic pain. *Front Mol Neurosci*. 2022;15:1007889. doi:10.3389/fnmol.2022.1007889
130. Tian G, Luo X, Tang C, et al. Astrocyte contributes to pain development via MMP2-JNK1/2 signaling in a mouse model of complex regional pain syndrome. *Life Sci*. 2017;170:64–71. doi:10.1016/j.lfs.2016.11.030
131. Stucky CL, Mikesell AR. Cutaneous pain in disorders affecting peripheral nerves. *Neurosci Lett*. 2021;765:136233. doi:10.1016/j.neulet.2021.136233
132. Talagas M, Lebonvallet N, Berthod F, Misery L. Cutaneous nociception: role of keratinocytes. *Exp Dermatol*. 2019;28(12):1466–1469. doi:10.1111/exd.13975
133. Moehring F, Cowie AM, Menzel AD, et al. Keratinocytes mediate innocuous and noxious touch via ATP-P2X4 signaling. *eLife*. 2018;7:e31684. doi:10.7554/eLife.31684
134. Sadler KE, Moehring F, Stucky CL. Keratinocytes contribute to normal cold and heat sensation. *eLife*. 2020;9:e58625. doi:10.7554/eLife.58625
135. Moehring F, Halder P, Seal RP, Stucky CL. Uncovering the cells and circuits of touch in normal and pathological settings. *Neuron*. 2018;100(2):349–360. doi:10.1016/j.neuron.2018.10.019
136. Talagas M, Lebonvallet N, Leschiera R, et al. Keratinocytes communicate with sensory neurons via synaptic-like contacts. *Ann Neurol*. 2020;88(6):1205–1219. doi:10.1002/ana.25912
137. Hou Q, Barr T, Gee L, et al. Keratinocyte expression of calcitonin gene-related peptide β : implications for neuropathic and inflammatory pain mechanisms. *Pain*. 2011;152(9):2036–2051. doi:10.1016/j.pain.2011.04.033
138. Li WW, Guo TZ, Li XQ, Kingery WS, Clark DJ. Fracture induces keratinocyte activation, proliferation, and expression of pro-nociceptive inflammatory mediators. *Pain*. 2010;151(3):843–852. doi:10.1016/j.pain.2010.09.026
139. Cirillo N. The local neuropeptide system of keratinocytes. *Biomedicines*. 2021;9(12):1854. doi:10.3390/biomedicines9121854

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