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REVIEW

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

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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

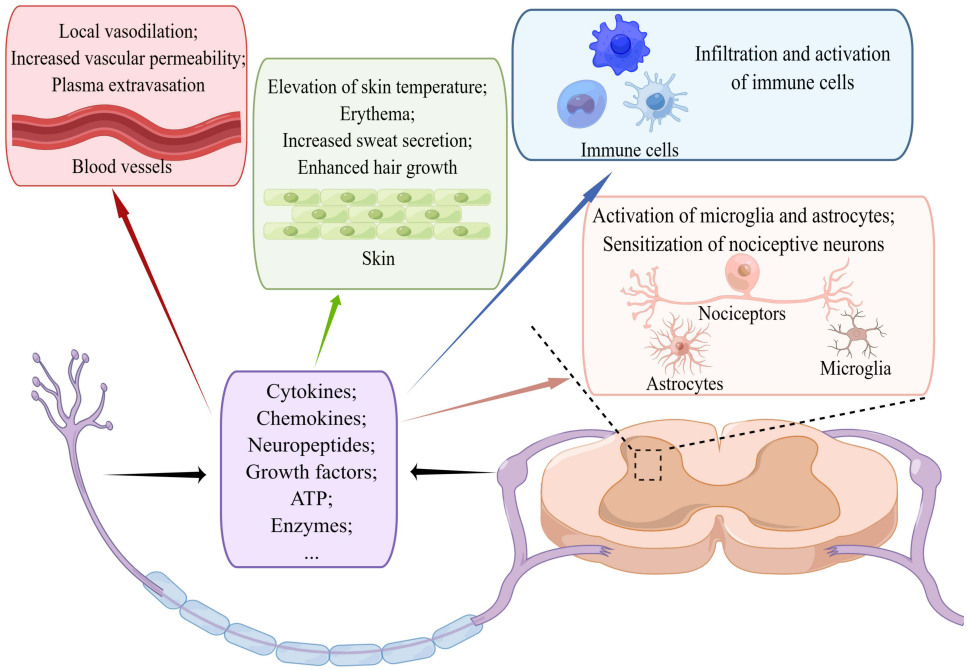

Figure 1 The role of neurogenic inflammation in the pathophysiology of CRPS. Nociceptive receptors can be activated by mechanical or chemical stimulation, leading to the release of cytokines, chemokines, neuropeptides, growth factors, ATP and enzymes. In the peripheral nervous system, these substances 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-1β 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-1β 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-1β, 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-1β prevented activation of glial cells in the SDH and reduced pain responses, revealing that IL-1β 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

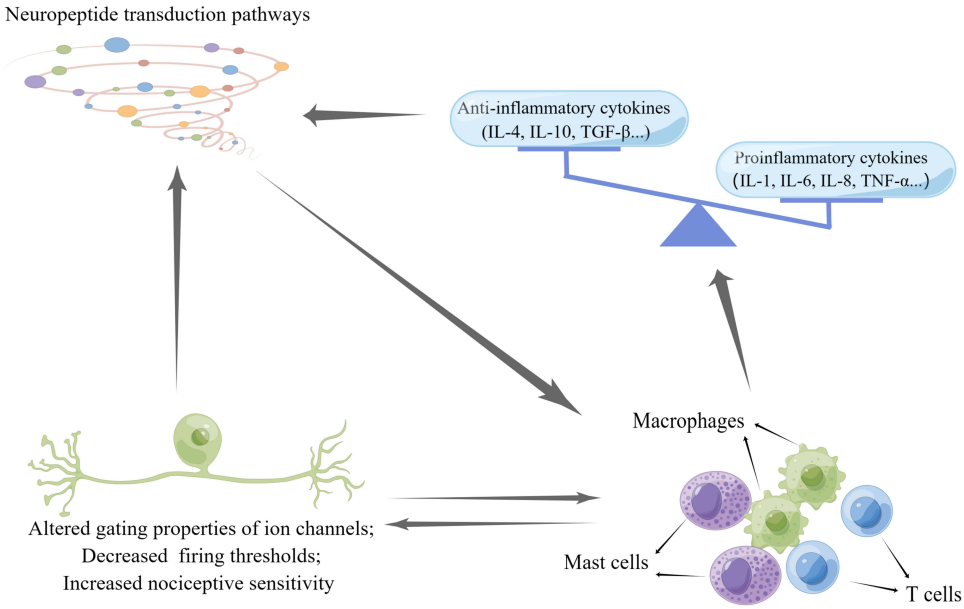

Figure 2 The role of cytokines and immune cells in the development of neuroinflammation in CRPS. Nociceptors release neuropeptides and neurotransmitters from their peripheral terminals, which activate immune responses. Immune cells infiltrate and produce numerous molecules that bind to receptors in nociceptors, 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-1β, 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 CPIP 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-1β, 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-1β, 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 Aδ 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-1β by keratinocytes was increased. However, administering an IL-1 receptor antagonist effectively relieved pain induced by these neuropeptides.[62] In CPIP 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 sensitization[59] (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-1β, 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

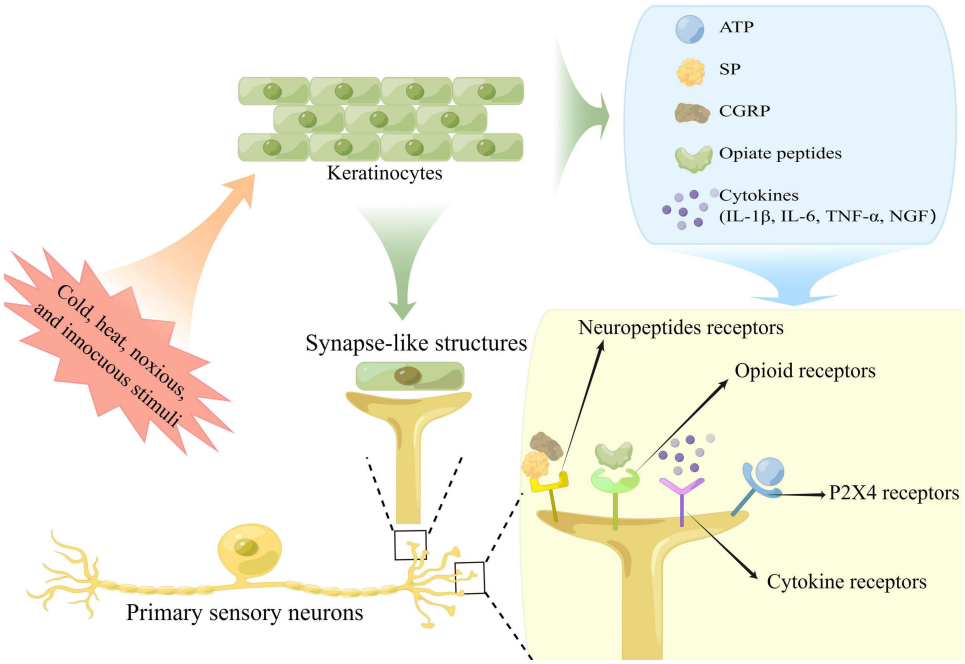

Figure 3 The role of keratinocytes in the development of neuroinflammation in CRPS. When exposed to various stimuli, such as cold, heat, and noxious and innocuous stimulation, keratinocytes can release ATP, SP, CGRP, IL-1β, IL-6, TNF-α and NGF to activate sensory nociceptors. Additionally, keratinocytes 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-1β, interleukin-1β; 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

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