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Neuroimmune Crosstalk in Chronic Pain Syndromes: Emerging Roles of Glial Cells and Cytokines

Serunjogi Ruth

Department of Clinical Pharmacy Kampala International University Uganda
Email: ruth.serunjogi@studwc.kiu.ac.ug

ABSTRACT

Chronic pain syndromes represent a significant global health burden, characterized by persistent pain that extends beyond normal tissue healing. Once considered a purely neuronal phenomenon, chronic pain is now recognized as a complex neuroimmune disorder involving bidirectional communication between the nervous system and immune components. Glial cells particularly microglia and astrocytes have emerged as key modulators of nociceptive signaling through their production of pro-inflammatory and anti-inflammatory cytokines. These cells, activated in response to peripheral nerve injury, infection, or inflammation, contribute to central sensitization by altering synaptic transmission and increasing neuronal excitability. Cytokines such as TNF-α, IL-1β, and IL-6 amplify pain signals, while regulatory cytokines including IL-10 can exert protective effects. This review synthesizes current evidence on the roles of glial activation and cytokine signaling in chronic pain pathophysiology, with an emphasis on neuropathic, inflammatory, and cancer-related pain. We also discuss novel therapeutic strategies targeting neuroimmune interactions, including glial inhibitors, cytokine blockers, and neuromodulatory approaches. Understanding neuroimmune crosstalk provides promising avenues for more precise and effective treatment strategies in chronic pain management.

Keywords: chronic pain, neuroimmune interaction, glial cells, cytokines, central sensitization, microglia, astrocytes

INTRODUCTION

Chronic pain is a complex and multifaceted condition that persists beyond the expected period of tissue healing and is commonly defined as pain lasting or recurring for more than three months [1]. Chronic pain is common worldwide and imposes substantial functional, psychological, and economic burdens [2]. Traditionally, the underlying mechanisms of chronic pain were thought to reside solely within neuronal circuitry, with a primary focus on peripheral nociceptors and central synaptic plasticity. However, accumulating evidence has redefined many chronic pain states as neuroimmune disorders characterized by extensive interactions among neurons, glial cells, and immune mediators [3,4]. The concept of neuroimmune crosstalk refers to bidirectional communication between neurons and non-neuronal cells, including immune cells resident in or recruited to the central nervous system (CNS) and peripheral nervous system (PNS) [3]. This interaction is highly dynamic and orchestrates both protective and pathological responses. Although acute immune responses after tissue injury or infection can facilitate healing and transient nociceptor sensitization, persistent activation promotes maladaptive changes that contribute to central sensitization and chronic pain [3, 5, 6]. Central to this process are glial cells, particularly microglia and astrocytes, which actively modulate pain signaling through the release of inflammatory mediators and direct interactions with neurons [5, 6]. Cytokines are key molecular messengers in this process and act on both neuronal and glial targets [3, 11]. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6) can heighten pain sensitivity and lower nociceptive thresholds [11]. Conversely, anti-inflammatory cytokines such as IL-10 can attenuate these effects, although endogenous counter-regulation is often insufficient in persistent pain states [12]. This review aims to dissect the

molecular and cellular mechanisms by which glial cells and cytokines contribute to the pathogenesis of chronic pain. It also addresses how these neuroimmune interactions vary across different chronic pain syndromes, including neuropathic, inflammatory, and cancer-related pain. Furthermore, the review evaluates emerging therapeutic strategies that specifically target these neuroimmune pathways, thereby opening new avenues for precision medicine in pain management. Understanding the intricacies of neuroimmune crosstalk is critical not only for elucidating the pathophysiology of chronic pain but also for informing the development of more effective, targeted, and sustainable therapeutic interventions. In the following sections, we delve deeper into the roles of glial activation and cytokine signaling in the chronic pain continuum.

Glial Cell Activation in Chronic Pain

Glial cells include microglia, astrocytes, and oligodendrocytes in the CNS, as well as satellite glial cells (SGCs) in peripheral sensory ganglia. Although once viewed mainly as support cells, glia are now recognized as active participants in the initiation and persistence of chronic pain [5,6]. These cells respond to neural injury, infection, or inflammation by adopting reactive states that alter their morphology, gene expression, and signaling functions. Microglia, the resident immune cells of the CNS, are among the earliest spinal glial responders after peripheral nerve injury [3,7,8]. Activated microglia show morphological changes, increased expression of markers such as Iba1 and CD11b, and release mediators including TNF-alpha, IL-1beta, IL-6, prostaglandins, and brain-derived neurotrophic factor (BDNF) [3,5,6]. This pro-inflammatory and neuromodulatory milieu increases the excitability of spinal dorsal horn neurons and can weaken inhibitory neurotransmission, both of which are central to pain sensitization [8,9,11]. Astrocytic activation often develops after the early microglial response and may persist during later phases of neuropathic pain [7]. Reactive astrocytes show hypertrophy, upregulation of glial fibrillary acidic protein (GFAP), and increased production of cytokines, chemokines, and reactive oxygen species [5]. Because astrocytes regulate extracellular ions, neurotransmitter recycling, and synaptic support, their dysfunction can disrupt glutamate homeostasis and inhibitory signaling in chronic pain circuits [5, 11]. Satellite glial cells in dorsal root ganglia envelop sensory neurons and form closely coupled neuron-glia units. After peripheral injury or inflammation, SGCs increase gap-junction coupling and release mediators such as ATP, nitric oxide, and cytokines, thereby promoting communication among neighboring sensory neurons and increasing primary-afferent excitability [10]. Interactions among peripheral glia, spinal microglia, astrocytes, neurons, and infiltrating immune cells can create self-reinforcing signaling loops that sustain pain [3, 5, 6]. Experimental disruption of glial signaling attenuates pain-like behaviors in several animal models, supporting glial pathways as potential therapeutic targets while also underscoring the need to define their temporal, spatial, and context-dependent functions [6, 10].

Role of Cytokines in Pain Sensitization

Cytokines are small secreted proteins that coordinate immune responses and are produced by immune cells, glial cells, and, in some contexts, neurons after tissue injury, infection, or stress. In chronic pain, cytokines contribute to peripheral and central sensitization by altering neuronal excitability, synaptic transmission, and glial activation [3, 11, 14]. The balance between pro-inflammatory and anti-inflammatory signaling helps determine whether an immune response resolves or becomes maladaptive. TNF-alpha is an early mediator of nociceptive sensitization and can strengthen excitatory synaptic transmission while weakening inhibitory signaling [11]. It also sensitizes peripheral nociceptors and contributes to mechanical allodynia and thermal hyperalgesia [11,14]. IL-1beta can act synergistically with TNF-alpha, promote cyclooxygenase-2 expression and prostaglandin E2 production, enhance NMDA-receptor-dependent excitation, and reduce GABAergic inhibition [11]. IL-6 signaling through gp130-associated pathways can also increase neuronal excitability and facilitate pain transmission in the spinal dorsal horn [11]. In contrast, anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-beta) can counterbalance pro-inflammatory signaling. IL-10 suppresses the production of TNF-alpha, IL-1beta, and IL-6 and can reduce inflammatory activation in microglia [12]. However, endogenous anti-inflammatory responses may be inadequate or poorly timed in chronic pain. Peripheral inflammation can also influence the CNS through circulating mediators, neural routes, endothelial signaling, and blood-brain barrier interfaces, thereby promoting central glial activation [3]. Persistent pro-inflammatory cytokine signaling can therefore sustain a self-reinforcing cycle of neuroinflammation and sensitization [3, 11]. Defining when and where individual cytokines act is essential for designing therapies that interrupt pathological signaling without broadly suppressing protective immune functions.

Neuroimmune Dynamics in Specific Pain Syndromes

The neuroimmune mechanisms that underlie chronic pain manifest differently across clinical pain syndromes, with variations in the activation patterns of glial cells and the cytokine milieu. Understanding these disease-specific features is essential for tailoring therapeutic strategies.

Neuropathic Pain

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system and may follow trauma, diabetes, chemotherapy, or infections such as HIV or herpes zoster [13]. A prominent experimental feature is

activation of spinal microglia after peripheral nerve injury [3, 8]. Microglial BDNF binds neuronal TrkB receptors and reduces expression or function of the potassium-chloride cotransporter KCC2, shifting the neuronal anion gradient and impairing inhibitory signaling [9]. Astrocytes can further sustain excitation through cytokine release and altered glutamate handling, while infiltrating immune cells add additional inflammatory signals in peripheral nerves, dorsal root ganglia, and the spinal cord [3, 5]. SGCs surrounding injured sensory neurons also release ATP and inflammatory mediators that increase peripheral excitability [10].

Inflammatory Pain

Inflammatory pain arises from immune activation associated with infection, tissue injury, or autoimmune disease. Conditions such as rheumatoid arthritis, inflammatory bowel disease, and endometriosis illustrate how persistent inflammation can drive nociceptive hypersensitivity. Activated macrophages, mast cells, neutrophils, and other immune cells release TNF-alpha, IL-6, prostaglandins, and additional mediators that sensitize nociceptors [14]. These mediators act on receptors and ion channels, including TRPV1 and voltage-gated sodium channels, to enhance pain signaling [14]. Persistent peripheral inflammation can also recruit spinal glial responses, increasing cytokine production and altering synaptic plasticity in central pain pathways [3, 5].

Cancer Pain

Cancer pain reflects overlapping mechanisms that include tumor-associated inflammation, tissue destruction, nerve injury, and treatment-related neuropathy [15]. Tumor and stromal cells release nerve growth factor and inflammatory mediators that sensitize nociceptors and can promote abnormal sensory-fiber sprouting [15, 17]. Platinum compounds, taxanes, and other anticancer agents can produce chemotherapy-induced peripheral neuropathy through direct neurotoxicity and neuroinflammatory mechanisms [16]. In bone metastases, osteoclast activity, acidic microenvironments, structural damage, and tumor-derived mediators activate or sensitize nociceptive fibers [17]. Central glial and cytokine responses may further amplify these inputs, although the relative contribution varies by cancer type, treatment, and disease stage [3, 5].

Therapeutic Implications

Recognition of neuroimmune crosstalk in chronic pain has stimulated treatment strategies aimed at glial cells and cytokine signaling. Unlike conventional analgesics, which primarily target neuronal excitability or peripheral inflammatory enzymes, these approaches seek to modify non-neuronal processes that contribute to pain chronification [3, 6]. Glial inhibitors have shown promise mainly in preclinical models. Minocycline, a tetracycline derivative with microglia-modulating actions, reduces mechanical allodynia and pro-inflammatory cytokine expression in experimental pain models [18]. Ibudilast, another proposed glial modulator, has been evaluated in opioid-dependent volunteers and reduced several subjective withdrawal symptoms in exploratory analyses, but its efficacy for chronic neuropathic pain remains unproven [19]. Translation of broadly acting glial inhibitors into routine pain care is limited by questions about cellular specificity, treatment timing, long-term safety, and differences between animal models and human disease [3, 6]. Cytokine-targeted therapies represent another avenue. Biologic agents that neutralize TNF-alpha or inhibit other inflammatory cytokine pathways are established treatments for inflammatory diseases such as rheumatoid arthritis and can reduce disease-associated inflammatory pain [20]. Their benefits in neuropathic or cancer pain are less consistent, reflecting the redundancy and context dependence of cytokine networks. IL-10 gene delivery has produced sustained antiallodynic effects in animal models, but this strategy remains experimental [21]. Future approaches will need to restore protective immune balance without causing generalized immunosuppression. Neuromodulation may also influence neuroimmune signaling. In animal models, spinal cord stimulation reduces neuropathic pain behavior together with spinal glial activation [22]. Vagus nerve stimulation can engage the cholinergic anti-inflammatory pathway and suppress systemic cytokine responses [23]. Clinical studies of noninvasive vagus nerve stimulation for chronic pain are promising but heterogeneous, so these approaches should not yet be regarded as established anti-neuroinflammatory treatments [24]. Emerging approaches include microRNA-based interventions [25], cell-based therapies using mesenchymal stem cells [26], and nanoparticle-mediated delivery of anti-inflammatory genes or mediators [27]. Most of these strategies remain at the preclinical or early translational stage. The future of chronic pain management may therefore involve carefully selected combinations of neuromodulation, immunomodulation, and targeted pharmacotherapy designed to interrupt pathological neuroimmune feedback while preserving normal host-defense and tissue-repair functions.

CONCLUSION

Chronic pain syndromes are driven by intricate interactions between neuronal and immune elements. Glial cells and cytokines form a critical axis of neuroimmune crosstalk, contributing to the initiation and maintenance of persistent pain states. Advances in understanding these mechanisms open the door to targeted, immune-modulating interventions that could revolutionize chronic pain treatment and restore quality of life for millions of sufferers.

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