Journal of Integrative Neuroscience

J. Integr. Neurosci. **2025**; 24(4): 25829
https://doi.org/10.31083/JIN25829

Review

The Role of Cytokines in Postherpetic Neuralgia

Yunyan Shen[1], Ping Lin[2,*]

[1]The Fourth School of Clinical Medicine, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China
[2]Department of Geriatrics, Hangzhou Third People's Hospital, 310009 Hangzhou, Zhejiang, China
*Correspondence: Yjlp1l@163.com (Ping Lin)
Academic Editor: Parisa Gazerani
Submitted: 24 July 2024 Revised: 2 October 2024 Accepted: 23 October 2024 Published: 24 April 2025

Abstract

Nerve injury is a significant cause of postherpetic neuralgia (PHN). It is marked by upregulated expression of cytokines secreted by immune cells such as tumor necrosis factor alpha, interleukin 1 beta (IL-1β), IL-6, IL-18, and IL-10. In neuropathic pain (NP) due to nerve injury, cytokines are important for the induction of neuroinflammation, activation of glial cells, and expression of cation channels. The release of chemokines due to nerve injury promotes immune cell infiltration, recruiting inflammatory cytokines and further amplifying the inflammatory response. The resulting disequilibrium in neuroimmune response and neuroinflammation leads to a reduction of nerve fibers, altered nerve excitability, and neuralgia. PHN is a typical NP and cytokines may induce PHN by promoting central and peripheral sensitization. Currently, treating PHN is challenging and research on the role of cytokine signaling pathways in PHN is lacking. This review summarizes the potential mechanisms of cytokine-mediated PHN and discusses the cytokine signaling pathways associated with the central and peripheral sensitization of PHN. By elucidating the mechanisms of cytokines, the cells and molecules that regulate cytokines, and their signaling systems in PHN, this review reveals important research developments regarding cytokines and their signaling pathways mediating PHN, highlighting new targets of action for the development of analgesic drugs.

Keywords: cytokine; neuropathic pain; postherpetic neuralgia; neuroimmune

1. Introduction

Neuropathic pain (NP) is a prevalent condition, affecting approximately 10.3% of individuals in the general population. Its incidence is notably higher in specific populations such as elderly patients with herpes zoster (HZ), patients with diabetes, and patients with cancer [1]. Studies indicated that 5–30% of HZ patients develop postherpetic neuralgia (PHN) [2], with more than 30% of these patients experiencing persistent neuralgia for more than 1 year. This chronic NP significantly reduces the quality of life, leading to sleep disorders, anxiety, depression, decreased physical function, and even debilitation [3]. Furthermore, it increases the economic burden on patients [4]. Consequently, PHN has become one of the most common chronic diseases affecting the quality of life and mental health of the elderly.

Indeed, a widely recognized contributor to NP is nerve injury. Neurons, the functional units of the nervous system, are capable of sensing stimuli, transmitting excitation, and activating corresponding brain regions to produce sensations. PHN, a typical form of NP associated with nerve injury, is also related to aging, immune deficiency, and genetic factors [5–7]. Nerve injury promotes the upregulation of inflammatory cytokines [8], activation of glial cells [9], and reduction of peripheral sensory nerve fibers [10,11]. Subsequently, the abnormal expression of various ion channels related to pain signaling pathways in neurons leads to central sensitization, which is the primary cause of increased neuronal excitability and NP [12–15]. However, although most adults infected with the varicella-zoster virus (VZV) experience some degree of nerve injury, not all HZ is accompanied by PHN, which might be a hint of the decline in immunity [16]. Therefore, events secondary to nerve injury, such as the release of chemokines by peripheral neuron cell bodies and Schwann cells, are likely to induce immune cell infiltration, further contributing to the development of NP [17–19]. From this perspective, nerve injury serves as the backdrop for the occurrence of PHN.

Although rodent models for exploring the pathogenesis of PHN, such as rat models induced by herpes simplex virus type 1 (HSV-1) and VZV, have been successfully constructed to the current time, there are differences in the pathways of PHN progression from viral latency to activated infection between these models and humans. Notably, so far, there have been no reports of constructed animal models that mimic the VZV reactivation process. Therefore, the development of a more reliable viral reactivation animal model that exhibits PHN-like herpetic pain is undoubtedly a major challenge we currently face. The pathogenesis of PHN is associated with nerve injury, and the generally accepted academic mechanism for the pathogenesis of PHN is central and peripheral sensitization, including abnormal activation of glial cells and dysfunction of ion channels. Meanwhile, although the pathogenesis of other NP may vary depending on their etiology, pathological processes such as nerve injury and abnormal ion channel function are always present. Given this, the study of other NP can undoubtedly provide a valuable reference for PHN. PHN, as a

chronic neuralgia triggered by VZV invasion of nerves, is essentially, like all neuralgia, closely related to nerve injury, whether this injury is caused by viral infection, immune response, or mechanochemical factors. However, our study of the role of cytokines in PHN remains limited and clinical evidence seems insufficient due to the many challenges still facing the construction of current animal models of PHN. To fill this gap, we drew on other NP research findings to provide further insights into the pathogenesis of PHN when exploring the role of cytokines in PHN.

The pathogenesis of PHN remains under investigation. A growing body of evidence has enhanced our understanding of the role of inflammatory mediators, such as interleukins (ILs), tumor necrosis factor alpha (TNF-α), ATP, and chemokines, in the mechanisms of NP [17,20–22]. However, systematic and comprehensive studies on the changes and mechanisms of cytokines in the pathogenesis of PHN are still lacking. This paper reviews the peripheral and central mechanisms of PHN by which cytokines mediate pain, and also discusses the signaling pathways involved in its pathogenesis.In this paper, the identification of cytokines and neuroglial cells as potential therapeutic targets for PHN is emphasized, along with suggestions for future research avenues focusing on PHN treatment.

2. Nerve Injury

PHN is a prevalent type of NP in clinical practice and remains one of the most challenging chronic pain to manage. It is triggered by infection with VZV, a neurotropic herpes virus that lies dormant in human peripheral sensory ganglia. Reactivation of VZV is related to cellular immunity, which is typically effective in preventing such reactivation. However, compromised immune responses, especially in the elderly, facilitates VZV reactivation from dorsal root ganglia (DRG) latency, spreading along peripheral nerves to the skin [23,24]. During viral replication, the immune system releases inflammatory mediators, including cytokines and chemokines [25]. This leads to inflammation, hemorrhagic necrosis, and neuronal loss in the affected DRG [26,27], resulting in nerve damage. The inflammatory changes following nerve damage lead to the infiltration of immune cells, which are consistent with observations in other animal models of peripheral nerve injury [28–31]. This causes spontaneous firing of peripheral neurons, lowered activation thresholds, and amplified incoming neural signals, manifesting as neuronal dysfunction and ectopic discharges [12–14,25]. Interestingly, in the chronic constriction injury (CCI) model [32], thermal hyperalgesia can still occur when the ligature is loosely applied without causing actual mechanical damage. This suggests that the inflammatory response and the release of inflammatory mediators, rather than nerve injury itself, are key to maintaining NP. Inhibiting the inflammatory response can reduce hyperalgesia [33], where the injection of exogenous inflammatory mediators can induce pain [34], supporting the idea that inflammatory mediators play a role in mediating NP. These mediators encompass cytokines, interferons, tumor necrosis factors, chemokines, and colony-stimulating factors. Their production is from immune cells [35] and from glial cells [18,36–38], providing a structural basis for the mechanism by which inflammatory mediators mediate NP. Thus, VZV reactivation in PHN serves as the etiological factor for nerve damage, with cytokines playing a crucial role in mediating NP.

3. Cytokines

3.1 Overview of Cytokines Associated with PHN

Cytokines are proteins with low molecular weight that possess diverse biological functions. These proteins are predominantly secreted by immune cells. Additionally, other cell types, including keratinocytes, dendritic cells in the skin, and neuroglia within the central nervous system (CNS), also contribute to cytokine secretion [39–41]. The release of these cytokines is typically triggered by injury and inflammation [42]. Cytokines exert their biological functions by binding to specific receptors, and regulating cell growth, differentiation, and tissue repair. They are particularly important in stress reactions such as injury, pain, and infection. The properties of cytokines are related to the microenvironment and most have dual effects in different situations [43]. IL-1β promotes neuronal sensitization [44,45]. Pro-inflammatory cytokines include IL-1, IL-6, IL-18 and TNF-α. ILs mainly participate in the proliferation, differentiation, and activation of immune cells, whereas TNF-α can activate cytotoxic T cells and promote the production of other cytokines, collectively enhancing the inflammatory response. Anti-inflammatory cytokines, such as IL-4, IL-10, soluble IL-2 receptor (sIL-2R) antagonists, and TNF-binding proteins, primarily inhibit inflammation to prevent excessive inflammatory responses that could damage the body. However, IL-10 additionally facilitates the activation and expansion of B cells [46], thereby sustaining autoimmune responses (Fig. 1 shows the inflammatory response of immune cells). Under pathological conditions, an imbalance in cytokine levels can contribute to disease progression. For instance, following nerve injury, cytokines secreted by immune cells exert direct effects on neural signaling by binding to homologous receptors on neurons, microglia, and astrocytes within the spinal cord, DRG, and brain. Neuronal activation is not solely dependent on receptor-mediated interactions and cellular contacts but is also regulated through a broader network influenced by cytokine activity [47]. Consequently, these cytokines establish a communication network between immune cells and neurons, involved in the modulation of neural responses [48].

Recent research indicates that PHN is often accompanied by an inflammatory response [10], evidenced by the presence of various cytokines at the injury site, adjacent areas, and even in the plasma [49,50]. These include TNF-α,

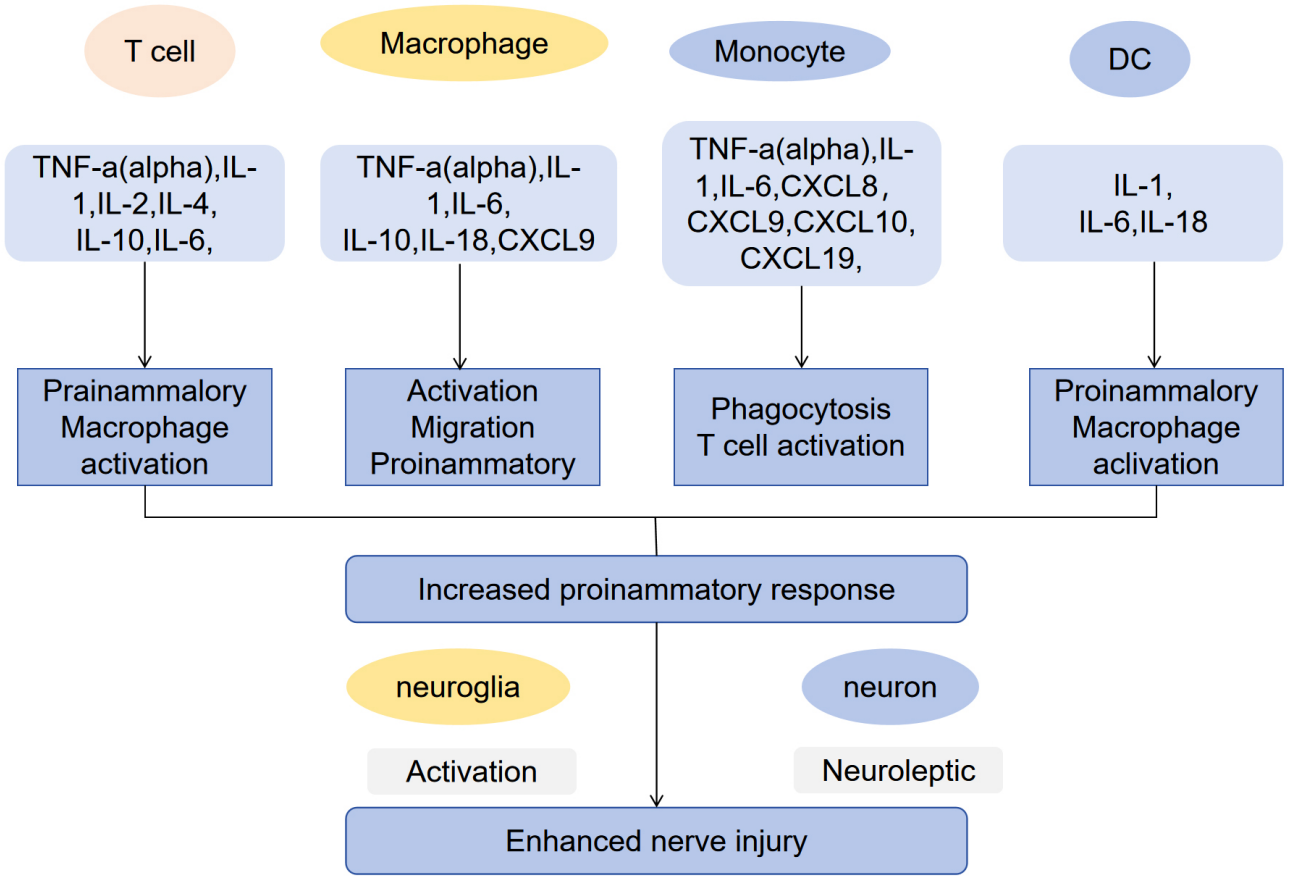

Fig. 1. The roles of immune cells and glial cells in amplifying the inflammatory response during nerve injury. Glial cells in the DRG and immune cells secrete inflammatory mediators. T cells, macrophages, and monocytes have been shown to infiltrate tissues infected by viruses. These cytokines promote the activation of glial cells and increase neuronal excitability. The interactions of neuroimmune and glial cells accelerate nerve injury, and promote pain generation. The figure was drawn using WPS office (12.1.0.20305, Kingsoft Office Software Co., LTD., Kowloon, Hong Kong, China). CXCL, C-X-C motifchemokine lingand; DC, dendritic cell; DRG, dorsal root ganglia; IL, Interleukin; TNF-α, tumor necrosis factor alpha.

ILs, interferon gamma (IFN-γ), various chemokines, and oxidative stress-related factors. Collectively, these factors are pivotal in the onset and advancement of NP. Among them, TNF-α, IL-1β, IL-6, IL-18, and IL-10 have been more extensively studied in relation to PHN. Other cytokines, such as IFN-γ, IL-2, IL-17 and IL-23, have been less well studied in relation to PHN. In untreated animal models [34,51–54], intrathecal injections of cytokines such as IL-1β, IL-18, TNF, and IL-6 have been observed to directly induce pro-nociceptive effects, leading to hyperalgesia. Cytokines are both important members of the immune system and mediators of pain-related signals. Specifically, TNF-α, IL-1β, and IL-6 have been implicated in the development of NP across animal models, including PHN. These cytokines, produced by both neuroglia and immune cells, share common functions such as mediating pain-related cation channel expression, amplifying inflammatory responses, and activating glial cells. In the context of nerve injury, inflammatory cytokines act on nociceptor terminals to initiate pain pathways [55]. Additionally, neuronal activation triggers reciprocal cytokine release, further promoting inflammation. Prolonged inflammation leads to altered sensory nerve fiber signaling, which persists even after inflammation and injury have healed. In summary, it can be hypothesized that cytokines are closely related to the development PHN. This paper explores the signaling pathways of TNF-α, IL-1, IL-6, IL-18, and IL-10, elucidating their roles in the pathogenesis of PHN.

3.2 Signaling of Cytokines

3.2.1 Overview of TNF-α Signaling

TNF-α is intricately involved in the pathogenesis of NP. This cytokine is primarily synthesized by macrophages and acts as a versatile systemic inflammatory mediator. Structurally, TNF-α comprises a signal peptide and two domains, existing in monomeric, dimeric, or trimeric forms, with dimers exhibiting the highest biological activity. Two different receptors, TNF receptor 1 (TNFR1) and TNFR2, are responsible for mediating TNF-α signaling [56]. TNFR1 is broadly expressed and can in-

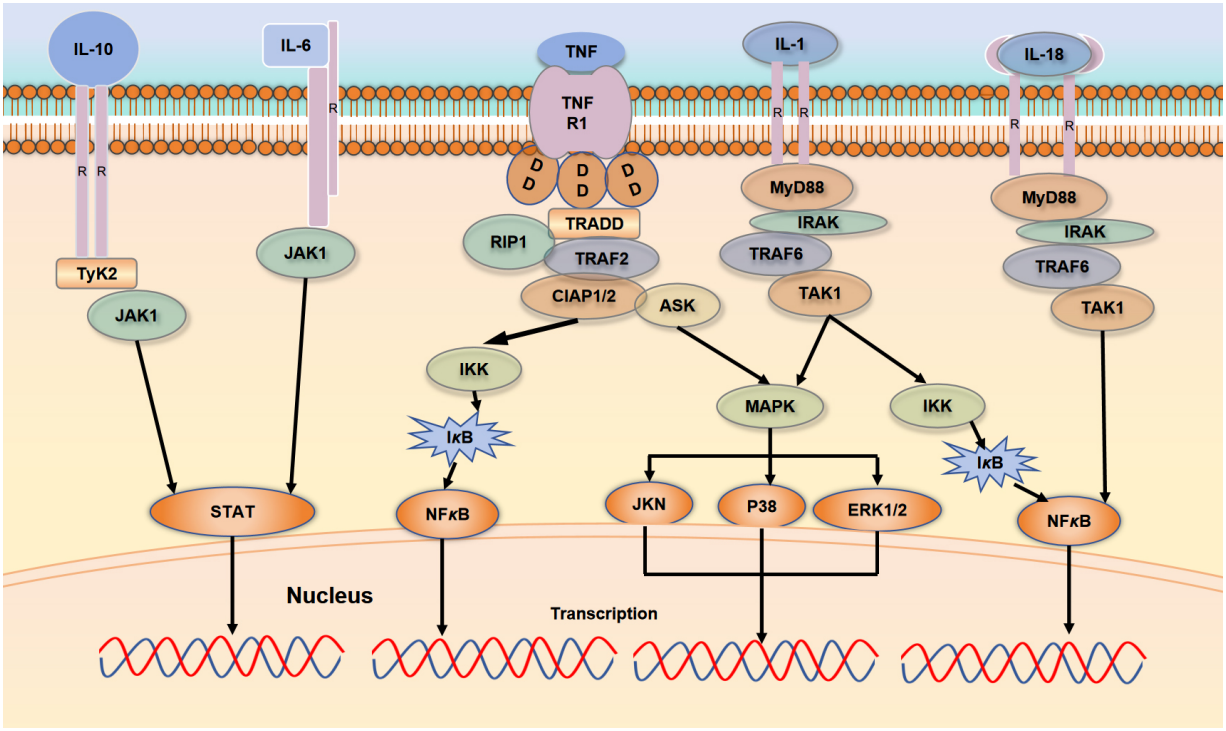

Fig. 2. TNF-α, IL-1β, IL-6, IL-18, and IL-10 exerts various biological effects through their interactions with specific receptors. Both TNF-α and IL-1β engage with their respective receptors, activating the NF-κB and MAPK signaling pathways; IL-6 and IL-10 activate the JAK/STAT pathway upon receptor binding, while IL-18 binds to its receptor to activate the NF-κB pathway. The figure was drawn using WPS office (12.1.0.20305, Kingsoft Office Software Co., LTD., Kowloon, Hong Kong, China). TNFR1, tumor necrosis factor receptor 1; TRADD, TNFR1-associated DD proteins; TRAF2, TNFR associated factor 2; TyK2, tyrosine kinase 2; IKK, IκB kinase; RIP1, receptor interacting serine/threonine protein kinase 1; CLAP, caspase recruitment domain-containing protein; ASK, apoptosis signal-regulating kinase; MAPK, Mitogen-Activated Protein Kinase; ERK, extracellular signal regulated kinase; TAK1, transforming growth factor β activated kinase 1; IRAK, interleukin receptor associated kinase.

Table 1. Cytokines, receptors and signaling pathways.

Cytokines	Receptors	Signaling Pathways	References
TNF-α	TNFR1	MAPK	[65]
		NF-κB	[66]
	TNFR2	Non-classical NF-κB	[60]
IL-1β	IL-1R	NF-κB, MAPK	[61]
IL-6	IL-6R	JAK-STAT3	[62]
IL-18	IL-18R	NF-κB	[63]
IL-10	IL-10R	JAK-STAT	[64]

IL-1R, IL-1 receptor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; STAT, signal transducers and activators of transcription.

duce apoptosis, while TNFR2 is predominantly found on specific cell types like immune and endothelial cells, involved mainly in anti-apoptotic signaling. TNF-α influences a variety of biological processes through its interaction with receptors TNFR1 and TNFR2. Through its interaction with TNFR1, TNF-α triggers the activation of the mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) pathways, initiating downstream signaling processes [57–59]. On the other hand, when TNF-α binds to TNFR2, it recruits TNF receptor-associated factor 2 (TRAF2) along with cellular inhibitors of apoptosis proteins 1 and 2 (cIAP1/2), thus activating the non-canonical NF-κB pathway (Table 1, Ref. [60–66]).

3.2.2 Overview of IL-1β Signaling

IL-1β, another cytokine, contributes to the initiation and advancement of NP. IL-1β is an inactive precursor peptide that undergoes cleavage and activation by IL-1β-converting enzyme caspase-1 during inflammation, leading to its extracellular secretion [67]. IL-1β initiates signal transduction primarily through the IL-1β R-associated kinase (IRAK) pathway. Upon binding, IL-1β forms a heterotrimeric complex with IL-1R type I (IL-1R1) and IL-1R accessory protein (IL-1RAcP). This interaction triggers the activation of IRAK4, resulting in IRAK4 autophosphorylation and phosphorylation of IRAK1 and IRAK2. Subsequently, TRAF6 is recruited and activated, which then activates members of the MAPK kinase kinase family. This cascade leads to NF-κB-inducing kinase phosphorylation, facilitating nuclear translocation of NF-κB and subsequent regulation of gene expression [68]. IL-1β signaling, similar

to TNF-α, activates both the NF-κB and p38-MAPK pathways, promoting the increased expression of genes such as IL-6, monocyte chemotactic protein-1, cyclooxygenase-2, IL-1α, and IL-1β [61].

3.2.3 Overview of IL-6 Signaling

IL-6 is a small molecular weight protein secreted by various immune cells. It transmits signals via the ligand-binding IL-6R alpha (IL-6Rα) and the signaling component gp130 (CD130) [69]. IL-6 signaling is primarily mediated through three main pathways: first, IL-6 binds to its receptor (IL-6R) to form a complex. This complex subsequently interacts with gp130, which activates intracellular signal transduction, ultimately leading to downstream signaling cascades and gene expression. sIL-6R binds to IL-6 and forms a complex with gp130, initiating signal transduction. Additionally, the interaction between IL-6 and the IL-6Rα-gp130 complex initiates signal transduction via Janus kinases (JAKs) and signal transducers and activators of transcription (STATs), which results in STAT3 phosphorylation, subsequent transcriptional activation in T cells, and the triggering of diverse biological effects [62].

3.2.4 Overview of IL-18 Signaling

IL-18 is a protein that mediates its action through a receptor belonging to the IL-1R family. The IL-18R on neurons and glial cells activates important signaling pathways. IL-18 binds to IL-18Rα, which then binds to IL-18Rβ to form a trimer [70–74]. The intracellular domain of IL-18R includes a Toll/IL-1R homology (TIR) domain, which is the same as that in Toll-like receptors. This TIR domain enables MyD88 to attach and relay signals into the cell. IL-18 activates the transcription factor NF-κB [63] and activator protein-1 (AP-1) through signaling molecules such as MyD88, IRAK, and TRAF6 (Table 1).

3.2.5 Overview of IL-10 Signaling

IL-10 exhibits analgesic effects and is secreted and recognized by a range of immune cells. Its main function *in vivo* is to suppress inflammation by downregulating the production of various pro-inflammatory factors. The functional IL-10R complex comprises a tetramer with two ligand-binding subunits and two auxiliary signaling subunits [75]. The canonical IL-10 signaling pathway involves the JAK/STAT pathway (Table 1) [64]. IL-10 binding to the extracellular domain of IL-10R1 triggers the phosphorylation of JAK1 and tyrosine kinase 2 (TYK2), which in turn activates the transcription factor STAT3. Furthermore, IL-10 reduces NF-κB activation by diminishing its DNA binding ability and inhibiting the activity of IκB kinase. Simultaneously, IL-10 activates AP-1 and NF-κB, promoting the differentiation of CD8+ T cells. In monocytes, IL-10 activates p85 triiodophosphate and p70 S6-kinases. However, blocking these pathways affects the proliferation-regulating activity of IL-10 but not its anti-inflammatory effects.

While these cytokines exhibit specificity in their biological functions depending on the microenvironment, they share common downstream signaling pathways. Notably, the MAPK and NF-κB signaling pathways play a significant role in pain sensitization, the expression of cation channels, and the processes of neuroinflammation. The activation of JAK enhances the sensitivity of the transient receptor potential vanilloid 1 (TRPV1), leading to peripheral sensitization. TNF-α is critical for Na^+ channel expression via the p38-MAPK pathway, which simultaneously stimulates the production of TNF-α by microglia. IL-1β influences pain transmission by modulating ion channels, including TRPV1 and the voltage-gated sodium channel alpha subunit 9 (Nav1.7), through activation of the NF-κB and p38-MAPK systems. IL-6 induces JAK and protein kinase C (PKC) activation, contributing to chronic pain. IL-18 promotes inflammation and increases pain sensitivity through NF-κB transcription. IL-10 may exert its effects by modulating these signaling pathways (Fig. 2).

4. The Role of Cytokines in PHN

Immune cells and glial cells produce a range of cytokines that contribute to both peripheral and central sensitization. Cytokines sustain pain signaling by influencing injury receptors and/or central spinal cord neurons. Cytokines upregulate the expression of pain-related cation channels, including Nav1.3, Nav1.7, Nav1.8, and Ca^{2+}, and to activate neuroglial cells. Increased levels of TNF-α , IL-6, and IL-1β, as well as other inflammatory mediators, have been observed at the site of nerve injury and in adjacent areas. Low concentrations of cytokines promote neuronal survival and growth and favor post-injury nerve repair, whereas high concentrations of cytokines induce neuronal apoptosis. The peripheral ends of injury receptors form tree-like structures in tissues and organs [76]. These sites are in close proximity to keratinocytes and immune cells and contribute to immunomodulation of injury receptor function. In the context of high-frequency afferent input resulting from tissue damage, a cascade of cytokines targets the ends of sensory nerve fibers known as injury receptors. This interaction initiates the activation of pain pathways, leading to neuronal activation and subsequent reciprocal stimulation of various cytokine-producing cells [55]. Notably, prolonged inflammation alters injury sensory processing, which persists even after inflammation and wound healing, creating a "neuropathic" like phenotype. In the CNS, the types of glial cells include astrocytes, oligodendrocytes, and microglia. Among them, astrocytes and microglia have been the focus of extensive research in the context of NP. It has been proposed that the p38-MAPK system can be activated by spinal astrocytes to promote pain sensitization [77]. Moreover, astrocytes regulate neuroplasticity [78]. Following inflammation, activated microglia undergo transformation into macrophage-like cells [79] that release cytokines such as TNF-α, IL-1β, IL-6, and IL-18, affecting synaptic sig-

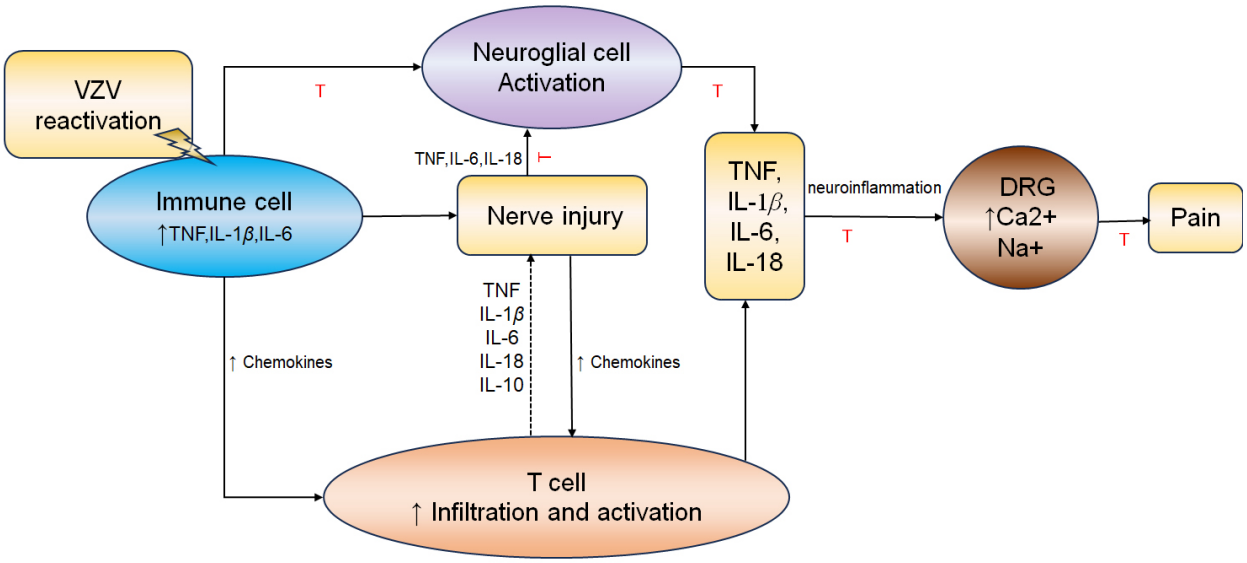

Fig. 3. Schematic representation of major interrelationships leading to nerve injury and pain. Upon VZV reactivation, immune cells secrete inflammatory mediators, including TNF, IL-1β and IL6, as well as chemokines. This inflammatory environment results in activation of glial cells and infiltration of immune cells, further amplifing the inflammatory response. These inflammatory cytokines, particularly TNF and IL-1β, induce the expression of pain-related cation channels in the DRG. This may lead to peripheral and central sensitization, promoting NP. Red inhibitory lines indicate possible options for targeted drug interventions. The figure was drawn using WPS office (12.1.0.20305, Kingsoft Office Software Co., LTD., Kowloon, Hong Kong, China). NP, neuropathic pain; VZV, varicella-zoster virus.

naling and pain transmission via the p38-MAPK system [80–82]. Cytokines released from glial cells at the spinal cord level can induce pain secondary to neuronal sensitization (Fig. 3).

4.1 TNF-α

In a meta-analysis study [83], TNF-α levels were evaluated in the body fluids of 113 participants, revealing higher TNF-α levels in patients with PHN compared to those who did not develop PHN after HZ. In a mouse model of PHN induced by HSV-1, elevated TNF-α levels were linked to PHN [12,25]. These findings indicate that increased TNF-α levels are linked to the occurrence of PHN. Strangfeld *et al.* [84] observed an increased risk of HZ with the use of TNF-α inhibitors [85]. Interestingly, among patients who developed HZ while using TNF-α inhibitors, there was a lower subsequent incidence of PHN, suggesting a potential role for TNF-α in PHN development. An experimental study has demonstrated that intrathecal injection of exogenous TNF-α can promote pain-induced hyperalgesia and mechanical allodynia [34]. Conversely, TNF-α inhibitors administered via the same route can alleviate chronic pain [86]. This further confirms the crucial role of TNF-α in the pathogenesis of PHN. Consequently, TNF-α inhibitors emerge as promising candidates for the management of chronic pain associated with PHN.

At low concentrations, TNF-α promotes neuronal survival and growth, whereas at high concentrations, TNF-α induces neuronal apoptosis. In the CCI model of rat sciatic nerve-induced NP, TNF-α expression is detected at the injury site [87]. Similar results have been observed in biopsies of human NP lesions [88]. Exogenous TNF-α injected into the DRG of CCI roots causes ectopic pain, suggesting that the cause of NP is not the nerve injury itself, but rather the action of inflammatory mediators following nerve injury [28,32]. In NP models following nerve injury, TNF-α plays a pivotal role in activating other cytokines [89]. TNF-α binds to its receptors and promotes the activation of inflammatory cells via NF-κB, triggering an inflammatory cascade [90]. TNF-α binds to its receptor and activates the NF-κB signaling pathway to mediate aberrant expression of voltage-gated Na^+ channels (VGSCs) or Na^+ currents [91,92]. A study has shown that exogenous TNF-α administered around nerve leads to persistent mechanical allodynia [90]. Zang *et al.* [92] demonstrated that TNF-α induces the upregulation of Nav1.3 expression in the DRG by activating NF-κB, and intrathecal injection of an NF-κB inhibitor significantly alleviates mechanical allodynia induced by the perisciatic injection of recombinant rat TNF-α. This indicates that TNF-α mediates the expression of VGSCs in the DRG via the NF-κB system, contributing to the development of NP [93–95]. Furthermore, TNF-α enhances membrane cation conductance in a non-voltage-gated manner, resulting in overall neuronal hyperexcitability, further exacerbates NP [95].

TNF-α is involved as a pro-inflammatory cytokine in the interaction between neuroimmune cells and glial cells in sensory ganglia and is essential for the promotion of PHN [96,97]. Following ischemic, inflammatory, or traumatic nerve tissue damage, TNF-α rapidly increases in regions such as the spinal dorsal horn, locus coeruleus, and hippocampus [98–101]. TNF-α mediates the central mechanisms of NP through neuroglial cells. Immunofluorescence staining has demonstrated the presence of TNF-α on the surface of astrocytes. TNF-α, through G protein-coupled receptor C-X-C chemokine receptor type 4, triggers the production of IL-1, IL-6, and ATP. These substances increase neuronal activity, and contribute to NP [80,102]. The TNF/TNFR1 signaling pathway contributes to NP by downregulating inward rectifying K^+ channels (Kir4.1) in astrocytes, disrupting K^+ homeostasis. Microglial cells have been shown to participate in the pathogenesis of NP [103,104]. Following nerve injury and inflammation [80,105–108], activated microglia secrete pro-inflammatory cytokines mediated by the p38-MAPK system including TNF-α, IL-1, IL-6, C-C motif chemokine ligand 2, and C-X3-C motif chemokine ligand 1, affecting synaptic signal transmission and pain transmission. TNF-α promotes Na^+ ion influx and lowers excitability thresholds through activation of the p38-MAPK pathway, thereby contributing to NP [91]. For instance, spinal nerve injury in rats induces allodynia, accompanied by elevated levels of TNF-α and phosphorylated p38. Inhibitors of TNF-α or p38 can alleviate this allodynia. TNF-α binds to its receptor and activates the NF-κB signaling pathway, whereas activation of the N-methy1-D-aspartate (NMDA) receptor is associated with the expression of NF-κB [109]. NMDA receptors are involved in peripheral, spinal cord, and cerebral pain pathways by potentiating excitatory postsynaptic currents [110]. Thus, NMDA may be a potential therapeutic target for PHN.

TNF-α is an important mediator in the pathogenesis of NP in the CNS and the peripheral nervous system. It acts in concert with various mediators, including ILs, nerve growth factors, chemokines, and IFNs, coordinating pain signal transmission through the NMDA, ATP, and MAPK signaling pathways.

4.2 IL-1β

IL-1β, belonging to the IL-1 family, is primarily produced by activated macrophages and exhibits different biological effects. Zhao *et al.* [111] reported increased levels of IL-1 in the cerebrospinal fluid of patients with PHN. In a meta-analysis involving 1373 participants, researchers confirmed that in patients with HZ, the expression of IL-6 and IL-1β was higher in those who developed PHN than in those with HZ without PHN [83]. However, Cao *et al.* [112] used a protein array to examine 40 common inflammatory factors in the skin lesion tissues of patients with PHN and found that only IL-1α was significantly elevated, albeit with low specificity, whereas there was no difference in expression of the other 39 inflammatory factors, including IL-1β. The contradictory results might stem from differences in detection sites. The epidermis in skin affected by PHN exhibits increased thickness compared to normal skin, suggesting possible structural or molecular changes. Immunohistochemical data have consistently shown reduced nerve ending density in the epidermis of PHN skin [113–117]. While various cell types can express IL-1, barrier cells such as epithelial cells normally express high amounts of IL-1. The decreased IL-1 expression in PHN may be linked to cellular changes such as the loss of specific cell types in the affected skin. Moreover, the molecular pathological alterations observed in the skin affected by PHN could lead to decreased IL-1 expression. This indicates that the persistent and chronic pain experienced by PHN patients may not be directly linked to skin inflammation.

Under normal conditions, IL-1β expression is low. After peripheral nerve injury, IL-1β expression is elevated in glial cells, and certain immune cells within the spinal cord, leading to diverse effects on the nervous system. Similar to TNF-α, IL-1β signaling participates in pain through activation of the NF-κB and p38-MAPK pathways. In the peripheral DRG, IL-1β acts on TRPV1 and IL-1R to modulate pain sensitivity [118]. TRPV1, part of the TRP family, is closely associated with the perception of harmful stimuli and pain generation. Activation of TRPV1 can regulate Ca^{2+} influx through voltage-dependent Ca^{2+} channels (VDCCs) [119]. This process results in the release of neuropeptides and excitatory amino acids from nerve terminals, which ultimately leads to the perception of pain in the cortex [120]. JAK and PKC inhibitors alleviate sensitization of TRPV1. TRP inhibitors help prevent the release of injurious substances, paving the way for the discovery of novel analgesics. Upon binding to IL-1Rs, IL-1β also promotes prostaglandin synthesis, indirectly sensitizing pain receptors to induce pain. Biologically active IL-1β is formed from the precursor IL-1β by cleavage through certain enzymes, with matrix metalloproteinases (MMPs) playing a significant role in this process. Among these, MMPs affect the release of IL-1β. Increased activity of MMP9 and MMP2 due to nerve injury promotes cleavage of the IL-1β precursor, resulting in the formation of biologically active IL-1β. Inhibitors of MMP9 or MMP2 can reduce the biological activity of IL-1β, significantly alleviating NP behaviors in animals. In addition, at central sites, IL-1β induces nociceptive sensitization [109] by promoting the release of substance P from α-amino-3-hydroxy-5-methyl4-isoxazolepropionic acid or NMDA receptors [121], an ionotropic glutamate receptor mediating excitatory neurotransmitter transmission that plays a crucial role in the pain pathway. Activation of the NMDA receptor leads to Ca^{2+} inward flow, promoting central sensitization [122]. In conclusion, IL-1β promotes PHN by directly or indirectly increasing neuronal excitability. Modulation of

IL-1β, TRPV1 [123], and NMDA receptors may serve as new analgesic options to alleviate NP in patients with PHN.

Therefore, therapeutic blockade of these proteases holds promise for limiting the release of biologically active IL-1β and potentially alleviating neuropathic inflammation to achieve relief from NP.

4.3 IL-6

IL-6 is considered an early marker of injury, playing a regulatory role in both the immune and nervous systems. It suppresses immune function by inducing macrophages to release transforming growth factor beta (TGF-β), which modulates the acute phase inflammatory response [69]. Arruda *et al*. [124] observed elevated *IL-6* mRNA levels in the spinal dorsal and ventral horns of rats following peripheral nerve injury. Similarly, studies involving human brain vascular adventitial fibroblasts (HBVAFs) and human peripheral nerve cells infected with VZV revealed significant increases in IL-6 transcription and expression levels, which lead to the loss of integrity of vascular and neural barrier and continued viral replication [125–127].

Research has shown that patients with HZ who later develop PHN have significantly higher IL-6 levels than those who do not develop PHN [128]. This suggests that elevated IL-6 expression is associated with inflammatory responses leading to nerve damage and promoting the onset and progression of NP. Downregulation of IL-6 expression can significantly alleviate pain. Saxena *et al*. [129] observed that during the treatment of neuralgia in patients with *HZ*, *IL-6* mRNA expression was significantly decreased following substantial pain relief. Lin *et al*. [130] analyzed IL-6 levels in patients with PHN based on pain severity and found significant differences among different severity groups, with particularly elevated IL-6 levels in patients with severe pain. Furthermore, IL-6 levels are correlated with short-term prognosis in patients with PHN. However, a study by Zak-Prelich *et al*. [131] reported conflicting results, possibly due to a smaller sample size and a broader age range.

IL-6 is associated with peripheral mechanisms of pain onset. Under physiological conditions, low levels of IL-6 are beneficial for normal development and repair of the nervous system; however, excessive production of IL-6 can lead to neurological damage. A study has shown that direct injection of IL-6 into rodent joints results in sustained sensitization of injury-sensing C fibers [120]. IL-6-mediated inflammatory responses may be linked to pain hypersensitivity. Following peripheral nerve injury, IL-6 and IL-6R are highly expressed in neurons. Similar to IL-1β and TNF-α, IL-6 enhances Na^+ [132] and Ca^{2+} [133] currents in peripheral nerve terminals, triggering action potential firing. This increases membrane excitability and reducs the pain threshold, leading to peripheral sensitization. IL-6 also induces activation of JAK and PKC, increasing TRPV1 sensitivity and inducing pain [134,135].

IL-6 is a neurogenic signaling mediator that transmits injury signals to the CNS [117]. Microglia activation promotes the PHN. After nerve injury, IL-6 mediates NP through the JAK2/STAT3 and ciliary neurotrophic factor (CNTF)/STAT3 signaling pathway [136,137]. Activation of the JAK2/STAT3 pathway promotes microglia and astrocyte activation, leading to cytokine release and amplifying neuroinflammation. The initiation and progression of inflammatory cascades from the peripheral regions to CNS are mediated by the CNTF-STAT3-IL-6 signaling axis. Blocking the CNTF-STAT3-IL-6 pathway can alleviate nerve inflammation in the DRG and spinal cord, thereby reducing pain following injury [137]. Administering anti-IL-6 antibodies significantly reduces JAK2/STAT3 signaling and pain behavior in rats. Overall, these studies suggest that targeting IL-6 could be advantageous in alleviating inflammatory responses and modulating the impact on nociceptors.

4.4 IL-18

IL-18 is also a cytokine involved in the regulation of the immune response [71]. It has been shown to be associated with chronic pain, such as NP, osteoarthritis pain, and cancer pain [72–74]. Khazan *et al*. [138] confirmed that IL-18 levels are linked to the risk of PHN. At the peripheral site, IL-18 ,which produced by immune cells, stimulates the transcription of Toll-like receptors and NF-κB, promoting the release of inflammatory mediators and mediated pain signaling [139,140]. IL-18 modulates pain by influencing ion channels and receptors mediating pain in the nervous system [72,141]. Increased IL-18 expression has been observed in various models of NP resulting from nerve injury. IL-18 plays a pivotal role in NP regulation through injurious sensory transmission [141–144]. In addition, IL-18 is crucial in regulating the activity of glial cells [145–147]. Blocking the IL-18 signaling pathway inhibits glial cell hyperactivity and subsequent activation of Ca^{2+} dependent signaling pathways [148]. IL-18-mediated interactions between microglia and astrocytes are pivotal for NP [72]. Studies [53,144] have shown that microglia contribute to inflammation and NP by producing IL-18. Additionally, oligodendrocytes have been implicated in neuroinflammation via IL-18 production [149]. Immune-mediated inflammation significantly influences NP development, with IL-18 mediating microglial and astrocytic interactions that release proinflammatory cytokines, chemokines, and other signaling molecules [72], thereby amplifying pain signals and recruiting immune cells to injury sites [150]. Moreover, IL-18 triggers cytokine production through inflammatory vesicle complexes, further enhancing the immune response [151]. These findings collectively emphasize the critical role of IL-18 in the pathogenesis of PHN.

4.5 IL-10

Uçeyler *et al*. [152] showed that IL-10 gene expression increases immediately after nerve injury, with a secondary peak observed within 45 days. Khan *et al*. [153] found that minimal inflammation of peripheral nerves following injury had no significant effect on IL-10 levels in sciatic nerve of rats across four types of sciatic nerve injuries. Partial nerve injury decreased IL-10 levels in the affected nerves, whereas complete nerve transection increased IL-10 expression. This implies that IL-10's involvement in NP etiology may vary depending on the specific nature of the nerve injury. After nerve injury, IL-10 activates microglia in the CNS to mediate NP [154]. IL-10 stimulates G protein-coupled receptor 40, along with intracellular signaling pathways such as STAT3, leading to increased β-endorphin expression and secretion [155]. Sharma *et al*. [156] identified the expression of IL-10 receptors in cortical neurons, where they mediate neuroprotection through the activation of the PI3K/AKT and STAT3 pathways. Additionally, Huang *et al*. [157] demonstrated that IL-10 attenuates NP by downregulating Nav1.7 in the DRG of rats. Following sciatic nerve crush injury in mice [158] , IL-10 secretion by macrophages is increased, which subsequently lowers the levels of chemokines and cytokines. Additionally, IL-10 deficiency impairs axonal regeneration and hinders the recovery of nerve functions. Atkins *et al*. [159] studied the effects of IL-10 on nerve regeneration in anesthetized C57 Black-6 mice following left sciatic nerve sectioning and resealing with four extraneous nerve sutures. The authors injected IL-10 (125 or 500 ng) at the repair site before and after nerve sectioning. Their findings revealed that a low dose of IL-10 at the sciatic nerve repair site facilitated better axonal regeneration, whereas a high dose did not. This suggests that optimal levels of IL-10 promote nerve regeneration, while prolonged high levels are detrimental to nerve repair. A study has shown that the induction of VZV-specific T lymphocytes is accompanied by increased IL-10 expression [152].

Jenkins *et al*. [160] showed that elevated levels of IL-10 are involved in the immune response to certain viruses. The intensity of the inflammatory response triggered by VZV directly influences the production of IL-10, which increases proportionally to mitigate the inflammation. However, high IL-10 levels can inhibit T helper1-specific cell-mediated immunity, allowing the virus to spread more effectively. While IL-10 enhances anti-inflammatory effects, it can also prolong inflammation, explaining why chronically high IL-10 levels impede nerve damage repair. In a study seeking predictors of neuralgia duration in HZ patients [161], a marked elevation in IL-10 levels was observed in the serum of patients experiencing severe HZ. IL-10 were positively correlated with neuralgia duration and pain severity, leading to the conclusion that IL-10 levels are an independent risk factor for PHN. Although most studies suggest that IL-10 has a positive effect on relieving NP, NP in these studies was short-lived and mostly inflammatory. PHN is a chronic NP lasting more than 3 months, caused by nerve injury. Persistent elevation of IL-10 not only prolongs the inflammatory response but also impedes nerve repair. From this perspective, IL-10 may mediate the development of PHN. Future studies on the mechanism of IL-10 involvement in PHN are needed (Table 2, Ref. [72,80,90–92,95,102,110,119,120,132,133,141,152,162]).

5. Future Research Perspectives

Cytokines are essential for sustaining NP. PHN, as a typical NP, is closely associated with inflammatory cytokines. Cytokines are generally secreted by multiple cells and can act on various target cells. Moreover, a single cytokine can trigger its target cells to produce additional cytokines, initiating a cascade of effects. In fact, neuroinflammation, driven by the interplay between pro-inflammatory and anti-inflammatory cytokines, serves as a fundamental mechanism underlying the onset of PHN. The above-mentioned role of cytokines in PHN is unquestionable, but there are few studies on the effects of cytokine antibodies on PHN. Cell and organ culture models, as well as animal studies, have demonstrated promising outcomes with anti-cytokine medications and pathway inhibitors for alleviating NP. However, clinical evidence remains sparse regarding the role of anti-cytokine drugs in NP. Moreover, clinical trials [163–166] targeting TNF-α antagonists in sciatic neuropathy treatment have notably failed to eliminate NP. Given the complex interplay in neuroinflammatory balance, targeting specific cytokines poses a challenge. An alternative therapeutic approach may involve regulating the cytokine cascade more comprehensively through growth factors. In a clinical trial using ibudilast to treat diabetic NP, patients experienced effective pain relief [167] due to the fact that ibudilast inhibits the activation of glial cells and reduces the release of cytokines. Valerian theophylline reduces pain by inhibiting microglia activity [168]. Thus, future research targeting entire systems [169–174] such as inflammatory cytokines, chemokines, MAPK, and neuroglial cells is expected to emerge as promising avenues for comprehensive PHN treatment. Due to the strict human specificity of VZV, how to use VZV strains in rodent models to overcome this specific infection remains to be determined by researchers, which will also provide reliable models for PHN treatment research.

6. Conclusion

The mechanisms underlying the development of PHN are complex and involve many factors, with cytokines playing a critical role. Cytokine-induced neuroinflammation is the root factor promoting PHN. As important molecules in neuroimmunity, cytokines regulate pain signaling pathways in both the peripheral nervous systems and CNS, activate glial cells, and increase neuronal excitability, thus promoting the development of PHN. Given that cytokines are cru-

Table 2. Possible mechanisms of action of cytokines involved in PHN.

Cytokines	Mechanisms of action	Effect	Refrences
TNF-α	Activation of voltage-gated Na^+ and Ca^{2+} channels	Central sensitization	[91,92,95]
	Increased excitatory postsynaptic membrane currents	Increases neuronal excitability	[80,102]
	Increase in membrane cation conductance in non-voltage gated mode	Increases neuronal excitability	[95]
	Promotes the release of inflammatory factors	Amplifying the inflammatory response	[90]
	NR1 phosphorylation of the NMDA receptor	Hyperalgesia	[110]
	Increased cyclooxygenase 2 and PGI2 synthase in endothelial cells	Peripheral sensitization	[162]
IL-1β	Capsaicin receptor activation regulates Ca^{2+} inward flow via VDCC	Release of neuropeptides and excitatory amino acids from nerve endings	[119,120]
IL-6	Increased Na^+ and Ca^{2+} currents in injury receptor terminals	Peripheral sensitization	[132,133]
IL-18	Regulation of ion channels and receptors	Peripheral and central sensitization	[141]
	Activation of glial cells	Promotes inflammation and increases pain sensitivity	[72]
IL-10	Suppression of the immune response	Prolonged inflammatory response	[152]

IL, interleukin; NMDA, N-methyl-D-aspartic acid; PGI2, prostaglandin I2; VDCC, Voltage-dependent calcium channel; PHN, postherpetic neuralgia.

cial for nerve repair, rather than completely blocking cytokine production, targeting cytokine-dependent responses, such as neuronal excitability and neuroinflammation, could be a better treatment option for PHN. Moreover, since cytokines regulate pain in PHN patients through a complex network, future treatment strategies should target specific actions across multiple systems simultaneously. Therefore, further understanding of the effects of cytokines on changes in neuronal excitability, neuroinflammation and pain could help identify novel therapeutic targets, making it possible to effectively treat chronic pain in PHN patients without impairing nerve repair.

Abbreviations

PHN, postherpetic neuralgia; HZ, herpes zoster; VZV, varicella-zoster virus; HSV-1, herpes simplex virus type 1; TNF-α, tumor necrosis factor alpha; CCI, chronic constriction injury; ILs, interleukins; IFN-γ, interferon gamma; TNFR1, TNF receptor 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; cIAP1/2, cellular inhibitor of apoptosis proteins 1 and 2; IRAK, IL-1β receptor-associated kinase; IL-1R1, IL-1 receptor type I; IL-1RAcP, IL-1 receptor accessory protein; TRAF6, tumor necrosis factor receptor-associated factor 6; JAK, Janus kinases; STAT, signal transducers and activators of transcription; TIR, toll-IL-1 receptor; AP-1, activator protein-1; DRG, dorsal root ganglion; NMDA, N-menthy1-D-aspartic acid; VGSCs, voltage-gated sodium channels; TRPV1, transient receptor potential vanilloid subtype 1; VDCC, Voltage-dependent calcium channels; MMPs, matrix metalloproteinases; TGF-β, transforming growth factor beta.

Author Contributions

PL designed an overview. YS wrote the manuscript. PL contributed to editorial changes in the manuscript. YS contributed to literature research. YS modified the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to thank their mentor and colleagues.

Funding

This study was supported by a co-construction science and technology programme project of the Zhejiang Provincial Administration of Traditional Chinese Medicine Grant (No. GZY-ZJ-KJ-23088).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Bouhassira D. Neuropathic pain: Definition, assessment and epidemiology. Revue Neurologique. 2019; 175: 16–25. https://doi.org/10.1016/j.neurol.2018.09.016

[2] van Oorschot D, Vroling H, Bunge E, Diaz-Decaro J, Curran D, Yawn B. A systematic literature review of herpes zoster incidence worldwide. Human Vaccines & Immunotherapeutics. 2021; 17: 1714–1732. https://doi.org/10.1080/21645515.2020.1847582

[3] Mizukami A, Sato K, Adachi K, Matthews S, Holl K, Matsuki T, *et al*. Impact of Herpes Zoster and Post-Herpetic Neuralgia on Health-Related Quality of Life in Japanese Adults Aged 60 Years or Older: Results from a Prospective, Observational Cohort Study. Clinical Drug Investigation. 2018; 38: 29–37. https://doi.org/10.1007/s40261-017-0581-5

[4] Patil A, Goldust M, Wollina U. *Herpes zoster*: A Review of Clinical Manifestations and Management. Viruses. 2022; 14: 192. https://doi.org/10.3390/v14020192

[5] Johnson RW, Rice ASC. Clinical practice. Postherpetic neuralgia. The New England Journal of Medicine. 2014; 371: 1526–1533. https://doi.org/10.1056/NEJMcp1403062

[6] Nishizawa D, Iseki M, Arita H, Hanaoka K, Yajima C, Kato J, *et al*. Genome-wide association study identifies candidate loci associated with chronic pain and postherpetic neuralgia. Molecular Pain. 2021; 17: 1744806921999924. https://doi.org/10.1177/1744806921999924

[7] Forbes HJ, Thomas SL, Smeeth L, Clayton T, Farmer R, Bhaskaran K, *et al*. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. Pain. 2016; 157: 30–54. https://doi.org/10.1097/j.pain.0000000000000307

[8] Zhao X, Deng H, Feng Y, Wang Y, Yao X, Ma Y, *et al*. Immune-cell-mediated tissue engineering strategies for peripheral nerve injury and regeneration. Journal of Materials Chemistry. B. 2024; 12: 2217–2235. https://doi.org/10.1039/d3tb02557h

[9] Kong C, Du J, Bu H, Huang C, Xu F, Ren H. LncRNA KCNA2-AS regulates spinal astrocyte activation through STAT3 to affect postherpetic neuralgia. Molecular Medicine (Cambridge, Mass.). 2020; 26: 113. https://doi.org/10.1186/s10020-020-00232-9

[10] Guedon JMG, Yee MB, Zhang M, Harvey SAK, Goins WF, Kinchington PR. Neuronal changes induced by Varicella Zoster Virus in a rat model of postherpetic neuralgia. Virology. 2015; 482: 167–180. https://doi.org/10.1016/j.virol.2015.03.046

[11] Sasaki A, Inomata Y, Serizawa K, Andoh T, Kuraishi Y. Contribution of sensory C-fiber neuron injury to mechanical dynamic allodynia in a murine model of postherpetic neuralgia. Neuroreport. 2013; 24: 137–141. https://doi.org/10.1097/WNR.0b013e32835df4d9

[12] Silva CR, Melo BMS, Silva JR, Lopes AH, Pereira JA, Cecilio NT, *et al*. S100A9 plays a pivotal role in a mouse model of herpetic neuralgia via TLR4/TNF pathway. Brain, Behavior, and Immunity. 2020; 88: 353–362. https://doi.org/10.1016/j.bbi.2020.03.033

[13] Hiraga SI, Itokazu T, Nishibe M, Yamashita T. Neuroplasticity related to chronic pain and its modulation by microglia. Inflammation and Regeneration. 2022; 42: 15. https://doi.org/10.1186/s41232-022-00199-6

[14] Alles SRA, Smith PA. Etiology and Pharmacology of Neuropathic Pain. Pharmacological Reviews. 2018; 70: 315–347. https://doi.org/10.1124/pr.117.014399

[15] Ou M, Chen J, Yang S, Xiao L, Xiong D, Wu S. Rodent models of postherpetic neuralgia: How far have we reached? Frontiers in Immunology. 2023; 14: 1026269. https://doi.org/10.3389/fimmu.2023.1026269

[16] Zerboni L, Sen N, Oliver SL, Arvin AM. Molecular mechanisms of varicella zoster virus pathogenesis. Nature Reviews. Microbiology. 2014; 12: 197–210. https://doi.org/10.1038/nrmicro3215

[17] McMahon SB, Cafferty WBJ, Marchand F. Immune and glial cell factors as pain mediators and modulators. Experimental Neurology. 2005; 192: 444–462. https://doi.org/10.1016/j.expneurol.2004.11.001

[18] Thacker MA, Clark AK, Bishop T, Grist J, Yip PK, Moon LDF, *et al*. CCL2 is a key mediator of microglia activation in neuropathic pain states. European Journal of Pain (London, England). 2009; 13: 263–272. https://doi.org/10.1016/j.ejpain.2008.04.017

[19] Zhang ZJ, Jiang BC, Gao YJ. Chemokines in neuron-glial cell interaction and pathogenesis of neuropathic pain. Cellular and Molecular Life Sciences: CMLS. 2017; 74: 3275–3291. https://doi.org/10.1007/s00018-017-2513-1

[20] Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nature Reviews. Neuroscience. 2005; 6: 521–532. https://doi.org/10.1038/nrn1700

[21] Rogers KJ, Merrill AE. Pain, Pain, Go Away: Exploring the Role of the Immune System in Regulating Chronic Pain. Clinical Chemistry. 2022; 68: 863. https://doi.org/10.1093/clinchem/hvac013

[22] Raghuraman S, Xie JY, Giacobassi MJ, Tun JO, Chase K, Lu D, *et al*. Chronicling changes in the somatosensory neurons after peripheral nerve injury. Proceedings of the National Academy of Sciences of the United States of America. 2020; 117: 26414–26421. https://doi.org/10.1073/pnas.1922618117

[23] Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. The New England Journal of Medicine. 2000; 342: 635–645. https://doi.org/10.1056/NEJM200003023420906

[24] Kennedy PGE, Mogensen TH, Cohrs RJ. Recent Issues in Varicella-Zoster Virus Latency. Viruses. 2021; 13: 2018. https://doi.org/10.3390/v13102018

[25] Silva JR, Lopes AH, Talbot J, Cecilio NT, Rossato MF, Silva RL, *et al*. Neuroimmune-Glia Interactions in the Sensory Ganglia Account for the Development of Acute Herpetic Neuralgia. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2017; 37: 6408–6422. https://doi.org/10.1523/JNEUROSCI.2233-16.2017

[26] Laing KJ, Ouwendijk WJD, Koelle DM, Verjans GMGM. Immunobiology of Varicella-Zoster Virus Infection. The Journal of Infectious Diseases. 2018; 218: S68–S74. https://doi.org/10.1093/infdis/jiy403

[27] Liu Q, Han J, Zhang X. Peripheral and central pathogenesis of postherpetic neuralgia. Skin Research and Technology. 2024; 30: e13867. https://doi.org/10.1111/srt.13867

[28] Kingery WS, Castellote JM, Wang EE. A loose ligature-induced mononeuropathy produces hyperalgesias mediated by both the injured sciatic nerve and the adjacent saphenous nerve. Pain. 1993; 55: 297–304. https://doi.org/10.1016/0304-3959(93)90004-9

[29] Shir Y, Seltzer Z. A-fibers mediate mechanical hyperesthesia and allodynia and C-fibers mediate thermal hyperalgesia in a new model of causalgiform pain disorders in rats. Neuroscience Letters. 1990; 115: 62–67. https://doi.org/10.1016/0304-3940(90)90518-e

[30] Miao P, Madec K, Gong Y, Shen H, Eisenstat D, Melanson M, *et al*. Axotomy-induced up-regulation of tumor necrosis factor-alpha in the dorsal root ganglia. Neurological Research. 2008; 30: 623–631. https://doi.org/10.1179/174313208X289606

[31] Xu JT, Xin WJ, Zang Y, Wu CY, Liu XG. The role of tumor

necrosis factor-alpha in the neuropathic pain induced by Lumbar 5 ventral root transection in rat. Pain. 2006; 123: 306–321. https://doi.org/10.1016/j.pain.2006.03.011

[32] Maves TJ, Pechman PS, Gebhart GF, Meller ST. Possible chemical contribution from chromic gut sutures produces disorders of pain sensation like those seen in man. Pain. 1993; 54: 57–69. https://doi.org/10.1016/0304-3959(93)90100-4

[33] Clatworthy AL, Illich PA, Castro GA, Walters ET. Role of periaxonal inflammation in the development of thermal hyperalgesia and guarding behavior in a rat model of neuropathic pain. Neuroscience Letters. 1995; 184: 5–8. https://doi.org/10.1016/0304-3940(94)11154-b

[34] Gruber-Schoffnegger D, Drdla-Schutting R, Hönigsperger C, Wunderbaldinger G, Gassner M, Sandkühler J. Induction of thermal hyperalgesia and synaptic long-term potentiation in the spinal cord lamina I by TNF-α and IL-1β is mediated by glial cells. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2013; 33: 6540–6551. https://doi.org/10.1523/JNEUROSCI.5087-12.2013

[35] Liu JA, Yu J, Cheung CW. Immune Actions on the Peripheral Nervous System in Pain. International Journal of Molecular Sciences. 2021; 22: 1448. https://doi.org/10.3390/ijms22031448

[36] Adler JE, Nico L, VandeVord P, Skoff AM. Modulation of neuropathic pain by a glial-derived factor. Pain Medicine (Malden, Mass.). 2009; 10: 1229–1236. https://doi.org/10.1111/j.1526-4637.2009.00708.x

[37] Hansson E. Could chronic pain and spread of pain sensation be induced and maintained by glial activation? Acta Physiologica (Oxford, England). 2006; 187: 321–327. https://doi.org/10.1111/j.1748-1716.2006.01568.x

[38] Moss A, Beggs S, Vega-Avelaira D, Costigan M, Hathway GJ, Salter MW, *et al*. Spinal microglia and neuropathic pain in young rats. Pain. 2007; 128: 215–224. https://doi.org/10.1016/j.pain.2006.09.018

[39] Sauder DN. The role of epidermal cytokines in inflammatory skin diseases. The Journal of Investigative Dermatology. 1990; 95: 27S–28S. https://doi.org/10.1111/1523-1747.ep12505705

[40] Compston A, Zajicek J, Sussman J, Webb A, Hall G, Muir D, *et al*. Glial lineages and myelination in the central nervous system. Journal of Anatomy. 1997; 190 (Pt 2): 161–200. https://doi.org/10.1046/j.1469-7580.1997.19020161.x

[41] Lisak RP, Skundric D, Bealmear B, Ragheb S. The role of cytokines in Schwann cell damage, protection, and repair. The Journal of Infectious Diseases. 1997; 176 Suppl 2: S173–S179. https://doi.org/10.1086/513788

[42] Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. Nature Reviews. Immunology. 2019; 19: 433–447. https://doi.org/10.1038/s41577-019-0147-2

[43] Shachar I, Karin N. The dual roles of inflammatory cytokines and chemokines in the regulation of autoimmune diseases and their clinical implications. Journal of Leukocyte Biology. 2013; 93: 51–61. https://doi.org/10.1189/jlb.0612293

[44] Liu T, Jiang CY, Fujita T, Luo SW, Kumamoto E. Enhancement by interleukin-1β of AMPA and NMDA receptor-mediated currents in adult rat spinal superficial dorsal horn neurons. Molecular Pain. 2013; 9: 16. https://doi.org/10.1186/1744-8069-9-16

[45] Araldi D, Ferrari LF, Lotufo CM, Vieira AS, Athié MCP, Figueiredo JG, *et al*. Peripheral inflammatory hyperalgesia depends on the COX increase in the dorsal root ganglion. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110: 3603–3608. https://doi.org/10.1073/pnas.1220668110

[46] Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Critical Reviews in Immunology. 2012; 32: 23–63. https://doi.org/10.1615/critrevimmunol.v32.i1.30

[47] Lapato AS, Tiwari-Woodruff SK. Connexins and pannexins: At the junction of neuro-glial homeostasis & disease. Journal of Neuroscience Research. 2018; 96: 31–44. https://doi.org/10.1002/jnr.24088

[48] Gonçalves Dos Santos G, Delay L, Yaksh TL, Corr M. Neuraxial Cytokines in Pain States. Frontiers in Immunology. 2020; 10: 3061. https://doi.org/10.3389/fimmu.2019.03061

[49] Gershon AA, Breuer J, Cohen JI, Cohrs RJ, Gershon MD, Gilden D, *et al*. Varicella zoster virus infection. Nature Reviews. Disease Primers. 2015; 1: 15016. https://doi.org/10.1038/nrdp.2015.16

[50] Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. Pain. 2018; 159: 595–602. https://doi.org/10.1097/j.pain.0000000000001122

[51] Reeve AJ, Patel S, Fox A, Walker K, Urban L. Intrathecally administered endotoxin or cytokines produce allodynia, hyperalgesia and changes in spinal cord neuronal responses to nociceptive stimuli in the rat. European Journal of Pain (London, England). 2000; 4: 247–257. https://doi.org/10.1053/eujp.2000.0177

[52] Sung CS, Wen ZH, Chang WK, Ho ST, Tsai SK, Chang YC, *et al*. Intrathecal interleukin-1beta administration induces thermal hyperalgesia by activating inducible nitric oxide synthase expression in the rat spinal cord. Brain Research. 2004; 1015: 145–153. https://doi.org/10.1016/j.brainres.2004.04.068

[53] Yang Y, Li H, Li TT, Luo H, Gu XY, Lü N, *et al*. Delayed activation of spinal microglia contributes to the maintenance of bone cancer pain in female Wistar rats via P2X7 receptor and IL-18. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2015; 35: 7950–7963. https://doi.org/10.1523/JNEUROSCI.5250-14.2015

[54] 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. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2008; 28: 5189–5194. https://doi.org/10.1523/JNEUROSCI.3338-07.2008

[55] Miller RJ, Jung H, Bhangoo SK, White FA. Cytokine and chemokine regulation of sensory neuron function. Handbook of Experimental Pharmacology. 2009; 417–449. https://doi.org/10.1007/978-3-540-79090-7_12

[56] Wallach D, Varfolomeev EE, Malinin NL, Goltsev YV, Kovalenko AV, Boldin MP. TUMOR NECROSIS FACTOR RECEPTOR AND Fas SIGNALING MECHANISMS. Annual Review of Immunology. 1999; 17: 331–367. https://doi.org/10.1146/annurev.immunol.17.1.331

[57] Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. Nature Reviews. Immunology. 2003; 3: 745–756. https://doi.org/10.1038/nri1184

[58] Zelová H, Hošek J. TNF-α signalling and inflammation: interactions between old acquaintances. Inflammation Research. 2013; 62: 641–651. https://doi.org/10.1007/s00011-013-0633-0

[59] van Loo G, Bertrand MJM. Death by TNF: a road to inflammation. Nature Reviews. Immunology. 2023; 23: 289–303. https://doi.org/10.1038/s41577-022-00792-3

[60] Sethu S, Melendez AJ. New developments on the TNFα-mediated signalling pathways. Bioscience Reports. 2011; 31: 63–76. https://doi.org/10.1042/BSR20100040

[61] Chen X, Han R, Hao P, Wang L, Liu M, Jin M, *et al*. Nepetin inhibits IL-1β induced inflammation via NF-κB and MAPKs signaling pathways in ARPE-19 cells. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2018; 101: 87–93. https://doi.org/10.1016/j.biopha.2018.02.054

[62] Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. The Biochemical Journal.

2003; 374: 1–20. https://doi.org/10.1042/BJ20030407
[63] Xu L, Li K, Li J, Xu F, Liang S, Kong Y, *et al*. IL-18 serves as a main effector of CAF-derived METTL3 against immunosuppression of NSCLC via driving NF-κB pathway. Epigenetics. 2023; 18: 2265625. https://doi.org/10.1080/15592294.2023.2265625
[64] Pei Y, Cui X, Wang Y. Regulation of IL-10 expression and function by JAK-STAT in CD8$^+$ T cells. International Immunopharmacology. 2024; 128: 111563. https://doi.org/10.1016/j.intimp.2024.111563
[65] Li Z, Qi X, Zhang X, Yu L, Gao L, Kong W, *et al*. TRDMT1 exhibited protective effects against LPS-induced inflammation in rats through TLR4-NF-κB/MAPK-TNF-α pathway. Animal Models and Experimental Medicine. 2022; 5: 172–182. https://doi.org/10.1002/ame2.12221
[66] Chen G, Goeddel DV. TNF-R1 signaling: a beautiful pathway. Science (New York, N.Y.). 2002; 296: 1634–1635. https://doi.org/10.1126/science.1071924
[67] Garlanda C, Dinarello CA, Mantovani A. The interleukin-1 family: back to the future. Immunity. 2013; 39: 1003–1018. https://doi.org/10.1016/j.immuni.2013.11.010
[68] Gabay C, Lamacchia C, Palmer G. IL-1 pathways in inflammation and human diseases. Nature Reviews. Rheumatology. 2010; 6: 232–241. https://doi.org/10.1038/nrrheum.2010.4
[69] Kaur S, Bansal Y, Kumar R, Bansal G. A panoramic review of IL-6: Structure, pathophysiological roles and inhibitors. Bioorganic & Medicinal Chemistry. 2020; 28: 115327. https://doi.org/10.1016/j.bmc.2020.115327
[70] Yasuda K, Nakanishi K, Tsutsui H. Interleukin-18 in Health and Disease. International Journal of Molecular Sciences. 2019; 20: 649. https://doi.org/10.3390/ijms20030649
[71] Rex DAB, Agarwal N, Prasad TSK, Kandasamy RK, Subbannayya Y, Pinto SM. A comprehensive pathway map of IL-18-mediated signalling. Journal of Cell Communication and Signaling. 2020; 14: 257–266. https://doi.org/10.1007/s12079-019-00544-4
[72] Miyoshi K, Obata K, Kondo T, Okamura H, Noguchi K. Interleukin-18-mediated microglia/astrocyte interaction in the spinal cord enhances neuropathic pain processing after nerve injury. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2008; 28: 12775–12787. https://doi.org/10.1523/JNEUROSCI.3512-08.2008
[73] Ihim SA, Abubakar SD, Zian Z, Sasaki T, Saffarioun M, Maleknia S, *et al*. Interleukin-18 cytokine in immunity, inflammation, and autoimmunity: Biological role in induction, regulation, and treatment. Frontiers in Immunology. 2022; 13: 919973. https://doi.org/10.3389/fimmu.2022.919973
[74] Tsoukas P, Rapp E, Van Der Kraak L, Weiss ES, Dang V, Schneider C, *et al*. Interleukin-18 and cytotoxic impairment are independent and synergistic causes of murine virus-induced hyperinflammation. Blood. 2020; 136: 2162–2174. https://doi.org/10.1182/blood.2019003846
[75] Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annual Review of Immunology. 2001; 19: 683–765. https://doi.org/10.1146/annurev.immunol.19.1.683
[76] Goudet C, Marchand F. Editorial: Molecular mechanisms of nociception. Frontiers in Molecular Neuroscience. 2022; 15: 1025230. https://doi.org/10.3389/fnmol.2022.1025230
[77] Ji RR, Suter MR. p38 MAPK, microglial signaling, and neuropathic pain. Molecular Pain. 2007; 3: 33. https://doi.org/10.1186/1744-8069-3-33
[78] Seth P, Koul N. Astrocyte, the star avatar: redefined. Journal of Biosciences. 2008; 33: 405–421. https://doi.org/10.1007/s12038-008-0060-5
[79] Vilhardt F. Microglia: phagocyte and glia cell. The International Journal of Biochemistry & Cell Biology. 2005; 37: 17–21. https://doi.org/10.1016/j.biocel.2004.06.010
[80] Watkins LR, Maier SF. Glia: a novel drug discovery target for clinical pain. Nature Reviews. Drug Discovery. 2003; 2: 973–985. https://doi.org/10.1038/nrd1251
[81] Ren K, Dubner R. Neuron-glia crosstalk gets serious: role in pain hypersensitivity. Current Opinion in Anaesthesiology. 2008; 21: 570–579. https://doi.org/10.1097/ACO.0b013e32830edbdf
[82] Fitzsimmons BL, Zattoni M, Svensson CI, Steinauer J, Hua XY, Yaksh TL. Role of spinal p38alpha and beta MAPK in inflammatory hyperalgesia and spinal COX-2 expression. Neuroreport. 2010; 21: 313–317. https://doi.org/10.1097/WNR.0b013e32833774bf
[83] Yue J, Yao M. Humoral Cytokine Levels in Patients with Herpes Zoster: A Meta-Analysis. Journal of Pain Research. 2024; 17: 887–902. https://doi.org/10.2147/JPR.S449211
[84] Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, *et al*. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009; 301: 737–744. https://doi.org/10.1001/jama.2009.146
[85] Javed S, Kamili QUA, Mendoza N, Tyring SK. Possible association of lower rate of postherpetic neuralgia in patients on antitumor necrosis factor-α. Journal of Medical Virology. 2011; 83: 2051–2055. https://doi.org/10.1002/jmv.22182
[86] Ramesh G, MacLean AG, Philipp MT. Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediators of Inflammation. 2013; 2013: 480739. https://doi.org/10.1155/2013/480739
[87] George A, Buehl A, Sommer C. Wallerian degeneration after crush injury of rat sciatic nerve increases endo- and epineurial tumor necrosis factor-alpha protein. Neuroscience Letters. 2004; 372: 215–219. https://doi.org/10.1016/j.neulet.2004.09.075
[88] Empl M, Renaud S, Erne B, Fuhr P, Straube A, Schaeren-Wiemers N, *et al*. TNF-alpha expression in painful and nonpainful neuropathies. Neurology. 2001; 56: 1371–1377. https://doi.org/10.1212/wnl.56.10.1371
[89] Shamash S, Reichert F, Rotshenker S. The cytokine network of Wallerian degeneration: tumor necrosis factor-alpha, interleukin-1alpha, and interleukin-1beta. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2002; 22: 3052–3060. https://doi.org/10.1523/JNEUROSCI.22-08-03052.2002
[90] Wei XH, Zang Y, Wu CY, Xu JT, Xin WJ, Liu XG. Peri-sciatic administration of recombinant rat TNF-alpha induces mechanical allodynia via upregulation of TNF-alpha in dorsal root ganglia and in spinal dorsal horn: the role of NF-kappa B pathway. Experimental Neurology. 2007; 205: 471–484. https://doi.org/10.1016/j.expneurol.2007.03.012
[91] Jin X, Gereau RW, 4th. Acute p38-mediated modulation of tetrodotoxin-resistant sodium channels in mouse sensory neurons by tumor necrosis factor-alpha. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2006; 26: 246–255. https://doi.org/10.1523/JNEUROSCI.3858-05.2006
[92] Zang Y, He XH, Xin WJ, Pang RP, Wei XH, Zhou LJ, *et al*. Inhibition of NF-kappaB prevents mechanical allodynia induced by spinal ventral root transection and suppresses the re-expression of Nav1.3 in DRG neurons in vivo and in vitro. Brain Research. 2010; 1363: 151–158. https://doi.org/10.1016/j.brainres.2010.09.048
[93] Zhang XL, Ding HH, Xu T, Liu M, Ma C, Wu SL, *et al*. Palmitoylation of δ-catenin promotes kinesin-mediated membrane trafficking of Na_v1.6 in sensory neurons to promote neuropathic pain. Science Signaling. 2018; 11: eaar4394. https://doi.org/10.1126/scisignal.aar4394

[94] Leo M, Argalski S, Schäfers M, Hagenacker T. Modulation of Voltage-Gated Sodium Channels by Activation of Tumor Necrosis Factor Receptor-1 and Receptor-2 in Small DRG Neurons of Rats. Mediators of Inflammation. 2015; 2015: 124942. https://doi.org/10.1155/2015/124942

[95] Wu Z, Wang S, Gruber S, Mata M, Fink DJ. Full-length membrane-bound tumor necrosis factor-α acts through tumor necrosis factor receptor 2 to modify phenotype of sensory neurons. Pain. 2013; 154: 1778–1782. https://doi.org/10.1016/j.pain.2013.05.038

[96] Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain. 1995; 63: 289–302. https://doi.org/10.1016/0304-3959(95)00186-7

[97] Watkins LR, Maier SF. The pain of being sick: implications of immune-to-brain communication for understanding pain. Annual Review of Psychology. 2000; 51: 29–57. https://doi.org/10.1146/annurev.psych.51.1.29

[98] Ignatowski TA, Covey WC, Knight PR, Severin CM, Nickola TJ, Spengler RN. Brain-derived TNFalpha mediates neuropathic pain. Brain Research. 1999; 841: 70–77. https://doi.org/10.1016/s0006-8993(99)01782-5

[99] Covey WC, Ignatowski TA, Knight PR, Spengler RN. Brain-derived TNFalpha: involvement in neuroplastic changes implicated in the conscious perception of persistent pain. Brain Research. 2000; 859: 113–122. https://doi.org/10.1016/s0006-8993(00)01965-x

[100] Covey WC, Ignatowski TA, Renauld AE, Knight PR, Nader ND, Spengler RN. Expression of neuron-associated tumor necrosis factor alpha in the brain is increased during persistent pain. Regional Anesthesia and Pain Medicine. 2002; 27: 357–366. https://doi.org/10.1053/rapm.2002.31930

[101] Li X, Wang J, Wang Z, Dong C, Dong X, Jing Y, *et al*. Tumor necrosis factor-α of Red nucleus involved in the development of neuropathic allodynia. Brain Research Bulletin. 2008; 77: 233–236. https://doi.org/10.1016/j.brainresbull.2008.08.025

[102] Watkins LR, Hutchinson MR, Milligan ED, Maier SF. "Listening" and "talking" to neurons: implications of immune activation for pain control and increasing the efficacy of opioids. Brain Research Reviews. 2007; 56: 148–169. https://doi.org/10.1016/j.brainresrev.2007.06.006

[103] Terayama R, Omura S, Fujisawa N, Yamaai T, Ichikawa H, Sugimoto T. Activation of microglia and p38 mitogen-activated protein kinase in the dorsal column nucleus contributes to tactile allodynia following peripheral nerve injury. Neuroscience. 2008; 153: 1245–1255. https://doi.org/10.1016/j.neuroscience.2008.03.041

[104] Wen YR, Suter MR, Ji RR, Yeh GC, Wu YS, Wang KC, *et al*. Activation of p38 mitogen-activated protein kinase in spinal microglia contributes to incision-induced mechanical allodynia. Anesthesiology. 2009; 110: 155–165. https://doi.org/10.1097/ALN.0b013e318190bc16

[105] Guedes RP, Araújo ASR, Janner D, Belló-Klein A, Ribeiro MFM, Partata WA. Increase in reactive oxygen species and activation of Akt signaling pathway in neuropathic pain. Cellular and Molecular Neurobiology. 2008; 28: 1049–1056. https://doi.org/10.1007/s10571-008-9279-9

[106] Li L, Xian CJ, Zhong JH, Zhou XF. Effect of lumbar 5 ventral root transection on pain behaviors: a novel rat model for neuropathic pain without axotomy of primary sensory neurons. Experimental Neurology. 2002; 175: 23–34. https://doi.org/10.1006/exnr.2002.7897

[107] White FA, Jung H, Miller RJ. Chemokines and the pathophysiology of neuropathic pain. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 20151–20158. https://doi.org/10.1073/pnas.0709250104

[108] Abbadie C, Bhangoo S, De Koninck Y, Malcangio M, Melik-Parsadaniantz S, White FA. Chemokines and pain mechanisms. Brain Research Reviews. 2009; 60: 125–134. https://doi.org/10.1016/j.brainresrev.2008.12.002

[109] Oka T, Aou S, Hori T. Intracerebroventricular injection of interleukin-1 beta enhances nociceptive neuronal responses of the trigeminal nucleus caudalis in rats. Brain Research. 1994; 656: 236–244. https://doi.org/10.1016/0006-8993(94)91466-4

[110] Lee IO, Yukhananov R, Standaert DG, Crosby G. NMDA-R1 antisense oligodeoxynucleotides modify formalin-induced nociception and spinal c-Fos expression in rat spinal cord. Pharmacology, Biochemistry, and Behavior. 2004; 79: 183–188. https://doi.org/10.1016/j.pbb.2004.07.003

[111] Zhao W, Wang Y, Fang Q, Wu J, Gao X, Liu H, *et al*. Changes in neurotrophic and inflammatory factors in the cerebrospinal fluid of patients with postherpetic neuralgia. Neuroscience Letters. 2017; 637: 108–113. https://doi.org/10.1016/j.neulet.2016.11.041

[112] Cao S, Zhang D, Yuan J, Deng W, Wen S, Qin B, *et al*. Inflammatory cytokine expression in the skin of patients with postherpetic neuralgia. The Journal of International Medical Research. 2020; 48: 300060520929582. https://doi.org/10.1177/0300060520929582

[113] Rowbotham MC, Yosipovitch G, Connolly MK, Finlay D, Forde G, Fields HL. Cutaneous innervation density in the allodynic form of postherpetic neuralgia. Neurobiology of Disease. 1996; 3: 205–214. https://doi.org/10.1006/nbdi.1996.0021

[114] Buonocore M, Gatti AM, Amato G, Aloisi AM, Bonezzi C. Allodynic skin in post-herpetic neuralgia: histological correlates. Journal of Cellular Physiology. 2012; 227: 934–938. https://doi.org/10.1002/jcp.22804

[115] Truini A, Haanpaa M, Provitera V, Biasiotta A, Stancanelli A, Caporaso G, *et al*. Differential myelinated and unmyelinated sensory and autonomic skin nerve fiber involvement in patients with ophthalmic postherpetic neuralgia. Frontiers in Neuroanatomy. 2015; 9: 105. https://doi.org/10.3389/fnana.2015.00105

[116] Oaklander AL. The density of remaining nerve endings in human skin with and without postherpetic neuralgia after shingles. Pain. 2001; 92: 139–145. https://doi.org/10.1016/s0304-3959(00)00481-4

[117] Petersen KL, Rice FL, Farhadi M, Reda H, Rowbotham MC. Natural history of cutaneous innervation following herpes zoster. Pain. 2010; 150: 75–82. https://doi.org/10.1016/j.pain.2010.04.002

[118] Binshtok AM, Wang H, Zimmermann K, Amaya F, Vardeh D, Shi L, *et al*. Nociceptors are interleukin-1beta sensors. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2008; 28: 14062–14073. https://doi.org/10.1523/JNEUROSCI.3795-08.2008

[119] Shah S, Carver CM, Mullen P, Milne S, Lukacs V, Shapiro MS, *et al*. Local Ca^{2+} signals couple activation of TRPV1 and ANO1 sensory ion channels. Science Signaling. 2020; 13: eaaw7963. https://doi.org/10.1126/scisignal.aaw7963

[120] Cernit V, Sénécal J, Othman R, Couture R. Reciprocal Regulatory Interaction between TRPV1 and Kinin B1 Receptor in a Rat Neuropathic Pain Model. International Journal of Molecular Sciences. 2020; 21: 821. https://doi.org/10.3390/ijms21030821

[121] Baamonde A, Hidalgo A, Menéndez L. Involvement of glutamate NMDA and AMPA receptors, glial cells and IL-1β in the spinal hyperalgesia evoked by the chemokine CCL2 in mice. Neuroscience Letters. 2011; 502: 178–181. https://doi.org/10.1016/j.neulet.2011.07.038

[122] Ahmadpour N, Kantroo M, Stobart MJ, Meza-Resillas J, Shabanipour S, Parra-Nuñez J, *et al*. Cortical astrocyte N-methyl-D-aspartate receptors influence whisker barrel activity and sen-

sory discrimination in mice. Nature Communications. 2024; 15: 1571. https://doi.org/10.1038/s41467-024-45989-3

[123] Chahl LA. TRPV1 Channels in the Central Nervous System as Drug Targets. Pharmaceuticals (Basel, Switzerland). 2024; 17: 756. https://doi.org/10.3390/ph17060756

[124] Arruda JL, Sweitzer S, Rutkowski MD, DeLeo JA. Intrathecal anti-IL-6 antibody and IgG attenuates peripheral nerve injury-induced mechanical allodynia in the rat: possible immune modulation in neuropathic pain. Brain Research. 2000; 879: 216–225. https://doi.org/10.1016/s0006-8993(00)02807-9

[125] Jones D, Neff CP, Palmer BE, Stenmark K, Nagel MA. Varicella zoster virus-infected cerebrovascular cells produce a proinflammatory environment. Neurology(R) Neuroimmunology & Neuroinflammation. 2017; 4: e382. https://doi.org/10.1212/NXI.0000000000000382

[126] Jarosinski KW, Carpenter JE, Buckingham EM, Jackson W, Knudtson K, Moffat JF, *et al*. Cellular Stress Response to Varicella-Zoster Virus Infection of Human Skin Includes Highly Elevated Interleukin-6 Expression. Open Forum Infectious Diseases. 2018; 5: ofy118. https://doi.org/10.1093/ofid/ofy118

[127] Blackmon AM, Como CN, Bubak AN, Mescher T, Jones D, Nagel MA. Varicella Zoster Virus Alters Expression of Cell Adhesion Proteins in Human Perineurial Cells via Interleukin 6. The Journal of Infectious Diseases. 2019; 220: 1453–1461. https://doi.org/10.1093/infdis/jiz095

[128] Zhu SM, Liu YM, An ED, Chen QL. Influence of systemic immune and cytokine responses during the acute phase of zoster on the development of postherpetic neuralgia. Journal of Zhejiang University. Science. B. 2009; 10: 625–630. https://doi.org/10.1631/jzus.B0920049

[129] Saxena AK, Bhardwaj N, Chilkoti GT, Malik A, Thakur GK, Bajaj M, *et al*. Modulation of mRNA Expression of IL-6 and mTORC1 and Efficacy and Feasibility of an Integrated Approach Encompassing Cognitive Behavioral Therapy Along with Pregabalin for Management of Neuropathic Pain in Postherpetic Neuralgia: A Pilot Study. Pain Medicine (Malden, Mass.). 2021; 22: 2276–2282. https://doi.org/10.1093/pm/pnab142

[130] Lin D, Zhong C, Jiang Q, Huang A, Liu Y. Serum interleukin-6 levels are increased in post-herpetic neuralgia: a single-center retrospective study. Anais Brasileiros De Dermatologia. 2023; 98: 202–207. https://doi.org/10.1016/j.abd.2022.03.007

[131] Zak-Prelich M, McKenzie RC, Sysa-Jedrzejowska A, Norval M. Local immune responses and systemic cytokine responses in zoster: relationship to the development of postherpetic neuralgia. Clinical and Experimental Immunology. 2003; 131: 318–323. https://doi.org/10.1046/j.1365-2249.2003.02061.x

[132] Liu MX, Zhong J, Xia L, Dou NN, Li ST. IL-6 contributes to Na_v1.3 up-regulation in trigeminal nerve following chronic constriction injury. Neurological Research. 2020; 42: 504–514. https://doi.org/10.1080/01616412.2020.1747719

[133] Jeevakumar V, Al Sardar AK, Mohamed F, Smithhart CM, Price T, Dussor G. IL-6 induced upregulation of T-type Ca^{2+} currents and sensitization of DRG nociceptors is attenuated by MNK inhibition. Journal of Neurophysiology. 2020; 124: 274–283. https://doi.org/10.1152/jn.00188.2020

[134] Vellani V, Mapplebeck S, Moriondo A, Davis JB, McNaughton PA. Protein kinase C activation potentiates gating of the vanilloid receptor VR1 by capsaicin, protons, heat and anandamide. The Journal of Physiology. 2001; 534: 813–825. https://doi.org/10.1111/j.1469-7793.2001.00813.x

[135] Schnizler K, Shutov LP, Van Kanegan MJ, Merrill MA, Nichols B, McKnight GS, *et al*. Protein kinase A anchoring via AKAP150 is essential for TRPV1 modulation by forskolin and prostaglandin E2 in mouse sensory neurons. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2008; 28: 4904–4917. https://doi.org/10.1523/JNEUROSCI.0233-08.2008

[136] Lee JY, Park CS, Seo KJ, Kim IY, Han S, Youn I, *et al*. IL-6/JAK2/STAT3 axis mediates neuropathic pain by regulating astrocyte and microglia activation after spinal cord injury. Experimental Neurology. 2023; 370: 114576. https://doi.org/10.1016/j.expneurol.2023.114576

[137] Hu Z, Deng N, Liu K, Zhou N, Sun Y, Zeng W. CNTF-STAT3-IL-6 Axis Mediates Neuroinflammatory Cascade across Schwann Cell-Neuron-Microglia. Cell Reports. 2020; 31: 107657. https://doi.org/10.1016/j.celrep.2020.107657

[138] Khazan M, Nasiri S, Riahi SM, Robati RM, Hedayati M. Measurement of melatonin, indole-dioxygenase, IL-6, IL-18, ferritin, CRP, and total homocysteine levels during herpes zoster. Journal of Medical Virology. 2020; 92: 1253–1259. https://doi.org/10.1002/jmv.25484

[139] Miyazawa H, Wada T. Immune-mediated inflammatory diseases with chronic excess of serum interleukin-18. Frontiers in Immunology. 2022; 13: 930141. https://doi.org/10.3389/fimmu.2022.930141

[140] Suk K, Yeou Kim S, Kim H. Regulation of IL-18 production by IFN gamma and PGE2 in mouse microglial cells: involvement of NF-kB pathway in the regulatory processes. Immunology Letters. 2001; 77: 79–85. https://doi.org/10.1016/s0165-2478(01)00209-7

[141] Zhang YK, Huang ZJ, Liu S, Liu YP, Song AA, Song XJ. WNT signaling underlies the pathogenesis of neuropathic pain in rodents. The Journal of Clinical Investigation. 2013; 123: 2268–2286. https://doi.org/10.1172/JCI65364

[142] Pilat D, Piotrowska A, Rojewska E, Jurga A, Ślusarczyk J, Makuch W, *et al*. Blockade of IL-18 signaling diminished neuropathic pain and enhanced the efficacy of morphine and buprenorphine. Molecular and Cellular Neurosciences. 2016; 71: 114–124. https://doi.org/10.1016/j.mcn.2015.12.013

[143] Li SS, Zhang WS, Ji D, Zhou YL, Li H, Yang JL, *et al*. Involvement of spinal microglia and interleukin-18 in the anti-nociceptive effect of dexmedetomidine in rats subjected to CCI. Neuroscience Letters. 2014; 560: 21–25. https://doi.org/10.1016/j.neulet.2013.12.012

[144] Bian C, Wang ZC, Yang JL, Lu N, Zhao ZQ, Zhang YQ. Up-regulation of interleukin-23 induces persistent allodynia via CX3CL1 and interleukin-18 signaling in the rat spinal cord after tetanic sciatic stimulation. Brain, Behavior, and Immunity. 2014; 37: 220–230. https://doi.org/10.1016/j.bbi.2013.12.011

[145] Rojewska E, Piotrowska A, Jurga A, Makuch W, Mika J. Zaprinast diminished pain and enhanced opioid analgesia in a rat neuropathic pain model. European Journal of Pharmacology. 2018; 839: 21–32. https://doi.org/10.1016/j.ejphar.2018.09.001

[146] Long L, Zhong W, Guo L, Ji J, Nie H. Effect of Bufalin-PLGA Microspheres in the Alleviation of Neuropathic Pain *via* the CCI Model. Frontiers in Pharmacology. 2022; 13: 910885. https://doi.org/10.3389/fphar.2022.910885

[147] Piotrowska A, Kwiatkowski K, Rojewska E, Makuch W, Mika J. Maraviroc reduces neuropathic pain through polarization of microglia and astroglia - Evidence from in vivo and in vitro studies. Neuropharmacology. 2016; 108: 207–219. https://doi.org/10.1016/j.neuropharm.2016.04.024

[148] Liu S, Liu YP, Lv Y, Yao JL, Yue DM, Zhang MY, *et al*. IL-18 Contributes to Bone Cancer Pain by Regulating Glia Cells and Neuron Interaction. The Journal of Pain. 2018; 19: 186–195. https://doi.org/10.1016/j.jpain.2017.10.003

[149] Gustin A, Kirchmeyer M, Koncina E, Felten P, Losciuto S, Heurtaux T, *et al*. NLRP3 Inflammasome Is Expressed and Functional in Mouse Brain Microglia but Not in Astrocytes. PloS One. 2015; 10: e0130624. https://doi.org/10.1371/journal.pone.0130624

[150] Sideris-Lampretsas G, Malcangio M. Microglial heterogeneity in chronic pain. Brain, Behavior, and Immunity. 2021; 96: 279–289. https://doi.org/10.1016/j.bbi.2021.06.005

[151] Mortezaee K, Khanlarkhani N, Beyer C, Zendedel A. Inflammasome: Its role in traumatic brain and spinal cord injury. Journal of Cellular Physiology. 2018; 233: 5160–5169. https://doi.org/10.1002/jcp.26287

[152] Uçeyler N, Tscharke A, Sommer C. Early cytokine expression in mouse sciatic nerve after chronic constriction nerve injury depends on calpain. Brain, Behavior, and Immunity. 2007; 21: 553–560. https://doi.org/10.1016/j.bbi.2006.10.003

[153] Khan J, Ramadan K, Korczeniewska O, Anwer MM, Benoliel R, Eliav E. Interleukin-10 levels in rat models of nerve damage and neuropathic pain. Neuroscience Letters. 2015; 592: 99–106. https://doi.org/10.1016/j.neulet.2015.03.001

[154] Deng MY, Ahmad KA, Han QQ, Wang ZY, Shoaib RM, Li XY, *et al*. Thalidomide alleviates neuropathic pain through microglial IL-10/β-endorphin signaling pathway. Biochemical Pharmacology. 2021; 192: 114727. https://doi.org/10.1016/j.bcp.2021.114727

[155] Belo TCA, Santos GX, da Silva BEG, Rocha BLG, Abdala DW, Freire LAM, *et al*. IL-10/β-Endorphin-Mediated Neuroimmune Modulation on Microglia during Antinociception. Brain Sciences. 2023; 13: 789. https://doi.org/10.3390/brainsci13050789

[156] Sharma S, Yang B, Xi X, Grotta JC, Aronowski J, Savitz SI. IL-10 directly protects cortical neurons by activating PI-3 kinase and STAT-3 pathways. Brain Research. 2011; 1373: 189–194. https://doi.org/10.1016/j.brainres.2010.11.096

[157] Huang Y, Zhu L, Zhang W, Tang Q, Zhong Y. IL-10 alleviates radicular pain by inhibiting TNF-α/p65 dependent Nav1.7 up-regulation in DRG neurons of rats. Brain Research. 2022; 1791: 147997. https://doi.org/10.1016/j.brainres.2022.147997

[158] Siqueira Mietto B, Kroner A, Girolami EI, Santos-Nogueira E, Zhang J, David S. Role of IL-10 in Resolution of Inflammation and Functional Recovery after Peripheral Nerve Injury. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2015; 35: 16431–16442. https://doi.org/10.1523/JNEUROSCI.2119-15.2015

[159] Atkins S, Loescher AR, Boissonade FM, Smith KG, Occleston N, O'Kane S, *et al*. Interleukin-10 reduces scarring and enhances regeneration at a site of sciatic nerve repair. Journal of the Peripheral Nervous System: JPNS. 2007; 12: 269–276. https://doi.org/10.1111/j.1529-8027.2007.00148.x

[160] Jenkins DE, Redman RL, Lam EM, Liu C, Lin I, Arvin AM. Interleukin (IL)-10, IL-12, and interferon-gamma production in primary and memory immune responses to varicella-zoster virus. The Journal of Infectious Diseases. 1998; 178: 940–948. https://doi.org/10.1086/515702

[161] Fukuyasu A, Kamata M, Sy Hau C, Nagata M, Fukaya S, Hayashi K, *et al*. Serum interleukin-10 level increases in patients with severe signs or symptoms of herpes zoster and predicts the duration of neuralgia. The Journal of Dermatology. 2021; 48: 511–518. https://doi.org/10.1111/1346-8138.15818

[162] Kanda H, Kobayashi K, Yamanaka H, Okubo M, Noguchi K. Microglial TNFα Induces COX2 and PGI2 Synthase Expression in Spinal Endothelial Cells during Neuropathic Pain. eNeuro. 2017; 4: ENEURO.0064-17.2017. https://doi.org/10.1523/ENEURO.0064-17.2017

[163] Korhonen T, Karppinen J, Malmivaara A, Autio R, Niinimäki J, Paimela L, *et al*. Efficacy of infliximab for disc herniation-induced sciatica: one-year follow-up. Spine. 2004; 29: 2115–2119. https://doi.org/10.1097/01.brs.0000141179.58778.6c

[164] Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Järvinen S, *et al*. The treatment of disc herniation-induced sciatica with infliximab: results of a randomized, controlled, 3-month follow-up study. Spine. 2005; 30: 2724–2728. https://doi.org/10.1097/01.brs.0000190815.13764.64

[165] Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Bowman C, *et al*. The treatment of disc-herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. Spine. 2006; 31: 2759–2766. https://doi.org/10.1097/01.brs.0000245873.23876.1e

[166] Cohen SP, Wenzell D, Hurley RW, Kurihara C, Buckenmaier CC, 3rd, Griffith S, *et al*. A double-blind, placebo-controlled, dose-response pilot study evaluating intradiscal etanercept in patients with chronic discogenic low back pain or lumbosacral radiculopathy. Anesthesiology. 2007; 107: 99–105. https://doi.org/10.1097/01.anes.0000267518.20363.0d

[167] Ledeboer A, Liu T, Shumilla JA, Mahoney JH, Vijay S, Gross MI, *et al*. The glial modulatory drug AV411 attenuates mechanical allodynia in rat models of neuropathic pain. Neuron Glia Biology. 2006; 2: 279–291. https://doi.org/10.1017/S1740925X0700035X

[168] Landry RP, Jacobs VL, Romero-Sandoval EA, DeLeo JA. Propentofylline, a CNS glial modulator does not decrease pain in post-herpetic neuralgia patients: in vitro evidence for differential responses in human and rodent microglia and macrophages. Experimental Neurology. 2012; 234: 340–350. https://doi.org/10.1016/j.expneurol.2011.11.006

[169] Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nature Reviews. Neuroscience. 2009; 10: 23–36. https://doi.org/10.1038/nrn2533

[170] Milligan ED, Sloane EM, Watkins LR. Glia in pathological pain: a role for fractalkine. Journal of Neuroimmunology. 2008; 198: 113–120. https://doi.org/10.1016/j.jneuroim.2008.04.011

[171] Bettoni I, Comelli F, Rossini C, Granucci F, Giagnoni G, Peri F, *et al*. Glial TLR4 receptor as new target to treat neuropathic pain: efficacy of a new receptor antagonist in a model of peripheral nerve injury in mice. Glia. 2008; 56: 1312–1319. https://doi.org/10.1002/glia.20699

[172] Schäfers M, Sommer C. Anticytokine therapy in neuropathic pain management. Expert Review of Neurotherapeutics. 2007; 7: 1613–1627. https://doi.org/10.1586/14737175.7.11.1613

[173] Gao YJ, Ji RR. Chemokines, neuronal-glial interactions, and central processing of neuropathic pain. Pharmacology & Therapeutics. 2010; 126: 56–68. https://doi.org/10.1016/j.pharmthera.2010.01.002

[174] Ji RR, Gereau RW, 4th, Malcangio M, Strichartz GR. MAP kinase and pain. Brain Research Reviews. 2009; 60: 135–148. https://doi.org/10.1016/j.brainresrev.2008.12.011