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Targeting cytokines for treatment of neuropathic pain

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Abstract

Background—Neuropathic pain is a challenging condition often refractory to existing therapies. An increasing number of studies have indicated that the immune system plays a crucial role in the mediation of neuropathic pain. Exploration of the various functions of individual cytokines in neuropathic pain will provide greater insight into the mechanisms of neuropathic pain and suggest potential opportunities to expand the repertoire of treatment options.

Methods—A literature review was performed to assess the role of pro-inflammatory and anti-inflammatory cytokines in the development of neuropathic pain. Both direct and indirect therapeutic approaches that target various cytokines for pain were reviewed. The current understanding based on preclinical and clinical studies is summarized.

Results and conclusions—In both human and animal studies, neuropathic pain has been associated with a pro-inflammatory state. Analgesic therapies involving direct manipulation of various cytokines and indirect methods to alter the balance of the immune system have been explored, although there have been few large-scale clinical trials evaluating the efficacy of immune modulators in the treatment of neuropathic pain. TNF- α is perhaps the widely studied pro-inflammatory cytokine in the context of neuropathic pain, but other pro-inflammatory (IL-1 β , IL-6, and IL-17) and anti-inflammatory (IL-4, IL-10, TGF- β) signaling molecules are garnering increased interest. With better appreciation and understanding of the interaction between the immune system and neuropathic pain, novel therapies may be developed to target this condition.

Keywords

Neuropathic pain; Immune modulation; Cytokines; Pro-inflammatory; Anti-inflammatory

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Ethical issues

None.

Conflict of interest

The authors declare that there is no conflict of interest.

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1. Introduction

Neuropathic pain refers to pain caused by pathology of the central or peripheral nervous system. It is a clinical diagnosis, typically described as shock-like or burning pain, often with hyperalgesia and allodynia [1,2]. A wide variety of painful conditions have a component of neuropathic pain, such as traumatic injury, nerve compression (e.g., radiculopathies, cancer metastases), metabolic disturbances (e.g., B12 deficiency, painful diabetic neuropathy), and infectious disease (e.g., post-herpetic neuralgia, HIV-associated neuropathy) [3].

Prior studies have suggested that dysregulation of neurotransmitters and over-excitation of ion channels responsible for signal transmission may contribute to the sensation of neuropathic pain [4,5]. Current first-line pharmacological treatments, antidepressants and anticonvulsants, target specific neurotransmitter receptors and ion channels to decrease neuropathic pain [2]. However, many patients continue to suffer from pain refractory to existing treatments. Therefore, better understanding of neuropathic pain mechanisms may offer alternative approaches to the management of neuropathic pain.

Recently, more studies have focused on the role of the immune system in neuropathic pain. In contrast to neuropathic pain, immune-mediated or inflammatory pain has classically been understood as pain secondary to inflammation from tissue damage [6]. Treatment approaches may differ depending on the type of pain identified. However, increasing evidence has demonstrated that inflammation at an affected nerve may play a role in mediating neuropathic pain [7,8]. Peripheral nerve damage activates glial cells, which release inflammatory mediators and stimulate production of pain signaling molecules (e.g., glutamate, substance P, calcitonin gene-related peptide); prolonged release of pro-inflammatory mediators can cause central nervous system changes that may result in neuropathic pain [9]. As various shared mechanisms are identified between the two types of pain, they warrant reconsideration of our understanding, diagnosis, and treatment of both neuropathic and inflammatory pain [10].

The signaling molecules of the immune system are cytokines, which can be broadly categorized as either pro-inflammatory or anti-inflammatory. Elevated pro-inflammatory cytokines have been associated with the presence of pain following nerve damage, whereas anti-inflammatory cytokines are associated with downregulation of the immune system and neuropathic pain relief [7,8,11]. In this review, we will provide a broad overview of the role of cytokines in modulating neuropathic pain and assess their potential therapeutic value in the treatment of this challenging pain disorder.

2. Targeting pro-inflammatory cytokines

Immune system activation has been shown to facilitate and increase neuropathic pain [12]. A number of pro-inflammatory cytokines, including TNF- α , IL-1 β , IL-6, and IL-17, have been found to be elevated in animal models of neuropathic pain. The same cytokines have also been found to be increased in the cerebrospinal fluid (CSF) and blood of patients with chronic neuropathic pain conditions [13–16]. Therefore, pharmacologically lowering the

levels of inflammatory cytokines may reduce pain, which has been demonstrated for various cytokines in both animal models and clinical studies (Table 1).

2.1. TNF- α

Tumor necrosis factor- α (TNF- α) is a cytokine first discovered in the context of facilitating cancer cell death [17]. Its involvement in neuropathic pain modulation has also been explored over the years. Studies have demonstrated that elevated TNF- α and its receptor are found at the sites of nerve damage in the classic chronic constriction injury (CCI) animal model of neuropathic pain [18–21]. Administration of exogenous TNF- α can also induce allodynia in rodents [22–26], while the administration of TNF- α antagonists has been found to decrease behaviors suggestive of pain and hyperalgesia in rodents following CCI [27–30].

Interestingly, the efficacy of TNF- α inhibitors seems to depend on the type of neuropathic pain. Despite promising findings in the CCI model as noted above, which is often considered a model of radiculopathy, TNF- α inhibitors have been shown to be only minimally effective in a rat disc-herniation model [31]. In contrast, TNF- α antagonists attenuated allodynia in diabetic mice, suggesting a possible treatment for diabetic neuropathy [32].

TNF- α inhibitors, including infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab, are currently FDA-approved for painful disorders such as inflammatory bowel disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis [33]. Clinical trials of TNF- α antagonists in patients with chronic neuropathic pain conditions have had mixed results. In pilot studies of patients diagnosed with severe sciatica, both intravenous and subcutaneous administration of a TNF- α inhibitor, either infliximab or etanercept, led to decreased pain scores and improved work status [34–37]. A placebo-controlled, dose-response study found that 14 out of 18 patients with subacute lumbosacral radiculopathy who received 2, 4, or 6 mg of etanercept via transforaminal epidural injection reported long-term leg pain relief in at 1 and 6 months following administration, compared to only one out of six patients in the saline control group [38]. However, limitations of the study included the small sample size, unknown therapeutic dose range of etanercept, and the fact that non-responders in both the etanercept and control groups were not followed past 1 month, per study protocol. Given the heterogeneity of the low back pain population, it is possible that initial non-responders in both treatment groups could have later developed improvements in pain, independent of the study intervention. Subsequent randomized, controlled trials (RCTs) have suggested no long-term benefit of TNF- α inhibitors compared to placebo [39–41]. Korhonen et al. reported similar efficacy of infliximab infusion compared to placebo for pain and functional status in 40 sciatica patients at 3 months and 1 year [36]. In a larger trial of 84 patients with lumbosacral radiculopathy, Cohen et al. found that epidural steroids resulted in a larger reduction in leg pain than etanercept 4 mg or saline at 1 month, and that these differences were not statistically significant [41]. By contrast, a different RCT of 80 patients with lumbar spinal stenosis found that epidural administration of etanercept 10 mg was safe and more effective than dexamethasone in reducing low back and leg pain, although functional status 4 weeks was similarly improved between the two groups [42]. However, blinding in this study was not clear, there was no placebo group, all patients were

taking non-steroidal anti-inflammatory drugs (NSAIDs) concurrently with treatment, and follow-up was limited to only 4 weeks after treatment.

Despite promising early studies, the failure of RCTs to establish the clinical efficacy of TNF- α inhibitors in neuropathic pain may reflect insufficient data regarding the appropriate indication, dose, treatment duration, and route of administration to achieve meaningful clinical benefit. Furthermore, differences in duration of symptoms and mechanism of injury (e.g., traumatic vs. degenerative) could also affect the response to TNF- α antagonist treatment. Lastly, it is important to note that TNF- α inhibitors are generally safe and well-tolerated, even with long-term use [43]. A better understanding of the role of TNF- α in the mediation of neuropathic pain will help identify appropriate patients for TNF- α blockade and elucidate its potential value in the treatment of chronic pain.

2.2. IL-1 β

Interleukin 1 β (IL-1 β) is another pro-inflammatory cytokine associated with immune activation. Elevated levels of IL-1 β have been found in rats with chronic neuropathic pain, both peripherally and in areas of the brain, including the hippocampus, brainstem, and prefrontal cortex [44–48]. Moreover, administration of IL-1 β provokes allodynia in rats [49,50]. Possible mechanisms include activation of the dorsal root ganglion neurons and increased spinal cord activity [51–53]. Knockout mice without IL-1 β demonstrate no hyperalgesia following partial nerve injury, suggesting that IL-1 β is essential in mediating neuropathic pain [54]. Likewise, exogenous IL-1 β antibody also reduces allodynia in animal models of neuropathic pain [55–57]. Recent studies have shown that alternative approaches, such as administration of human umbilical cord-derived mesenchymal stem cells (HUC-MSCs) and electroacupuncture, can decrease IL-1 β levels, suggesting a possible mechanism for their attenuation of pain [58,59]. While canakinumab, an IL-1 β inhibitor, has been FDA-approved for other conditions such as juvenile idiopathic arthritis, there have been no published studies on its use in chronic pain patients.

2.3. IL-6

Interleukin 6 (IL-6) appears to be associated with neuropathic pain, but its precise role is not well-understood. Early animal studies have shown that there is a local increase in IL-6 mRNA and protein levels following peripheral nerve injury [60–63]. Further studies have suggested that the upregulation of IL-6 may be through a prostaglandin E2-stimulated pathway [64,65]. However, in a rat nerve compression experiment, onset of allodynia immediately followed the compressing injury, whereas IL-6 elevation was delayed [66]. In addition to the temporal discrepancy, a spatial inconsistency has also been suggested. Following unilateral lumbar CCI in rats, elevated IL-6 was not only detected in the area of nerve injury, but also on the opposite side and in cervical regions, suggesting that IL-6 may be a non-specific marker of neuroinflammation, as opposed to a mediator of pain [67,68]. Nonetheless, reduction in IL-6 has been found to alleviate neuropathic pain in animals. IL-6 knockout mice had significantly less mechanical allodynia after nerve injury than control mice [69], and administration of anti-IL-6 antibody produces the same pain attenuation in rodents [70–72].

There have been several human studies of IL-6 in relation to neuropathic pain, with mixed results. Herniated vertebral disc samples obtained from patients showed elevated levels of numerous inflammatory markers, including IL-6 [73,74]. Two separate prospective cohort studies have suggested some benefit of tocilizumab, an anti-IL-6 antibody, in the treatment of sciatica and discogenic low back pain. Ohtori et al. reported that epidural administration of tocilizumab was safe and led to statistically significant improvements in low back and leg pain when compared to dexamethasone [75]. However, it is unclear whether this was a clinically significant benefit, particularly given that treatment blinding was not specified, there was no placebo group, all patients were on NSAIDs, and participants were only followed to 4 weeks after intervention. A more recent study from Sainoh et al. evaluated intradiscal tocilizumab bupivacaine versus bupivacaine only for discogenic back pain [76]. The authors reported statistically significant differences in pain relief and disability favoring tocilizumab at 2 and 4 weeks, but no difference at 6 weeks. However, these findings are difficult to interpret, since the study was neither blinded nor randomized, and there were significantly more males in the tocilizumab group. The investigators also noted that intradiscal pressure limited the dose administered, such that the actual dose of study drug varied by patient. However, the degree of dose variation was not reported. It is important to note that although no patients experienced complications in the epidural study, one patient who received intradiscal tocilizumab developed discitis [76]. Finally, in a six-year longitudinal study of patients with complex regional pain syndrome, authors found no association between IL-6 levels and symptoms [77].

2.4. IL-17

Rodent models of neuropathic pain induced by nerve ligation, CCI, and chemical injections, have all revealed an upregulation of interleukin 17 (IL-17), indicating its potential involvement in the development of allodynia [78–80]. The surge in IL-17 has been found to increase with time, suggesting that it may be part of the chronic pain phase, rather than the initial period of injury and acute pain [78,79]. Administration of exogenous IL-17 results in neuropathic pain, possibly secondary to an increase in the activity of transient receptor protein vanilloid 4 (TRPV4), an ion channel that has been found to mediate mechanical allodynia [81,82]. By contrast, IL-17 knockout mice showed less response to pain after induced nerve injury [83], and anti-IL-17 antibody injection has been demonstrated to decrease pain in a murine model of arthritis [84]. The IL-17 inhibiting monoclonal antibody, secukinumab, is FDA-approved for the treatment of plaque psoriasis, and it has been studied as a possible treatment in autoimmune diseases [85,86], but there are currently no human studies on the use of IL-17 antagonists in patients with neuropathic pain conditions.

3. Targeting anti-inflammatory cytokines

The immune system depends on the balance between pro-inflammatory and anti-inflammatory forces. Given that neuropathic pain is associated with a pro-inflammatory state, it is not surprising to find that high levels of anti-inflammatory cytokines are associated with a reduction in symptoms. Unfortunately, while anti-inflammatory cytokines offer an exciting new therapeutic opportunity for neuropathic pain, the current scientific evidence is limited to in vitro and animal studies.

Lower levels of anti-inflammatory cytokines have been demonstrated in patients with chronic neuropathic pain conditions, such as complex regional pain syndrome, atypical facial pain, lower back pain, and post-herpetic neuralgia [87,88]. Currently, there have been no published studies on whether treatments designed to increase anti-inflammatory cytokines can be used to reduce neuropathic pain in humans (Table 1).

3.1. IL-4

Interleukin 4 (IL-4) is an anti-inflammatory cytokine that has recently garnered attention as a mediator of neuropathic pain. IL-4 knockout mice demonstrate an increase in mechanical allodynia after CCI compared to controls [89]. Conversely, intrathecal injections of IL-4 in mice with CCI have been shown to reduce inflammation and levels of pro-inflammatory cytokines [90]. IL-4 treatment has also been found to reduce behavioral measures of mechanical allodynia after partial nerve ligation in mice [91].

Interestingly, glatiramer acetate, an immunomodulator used in the treatment of multiple sclerosis, has also been shown to decrease pain. Its use is correlated with an increase in IL-4 and IL-10, another anti-inflammatory cytokine [92]. These findings suggest that the anti-inflammatory pathway can be targeted to shift the immune environment and reduce neuropathic pain.

3.2. IL-10

Recent studies of interleukin 10 (IL-10) indicate an ambiguous relationship to neuropathic pain. Interestingly, IL-10 levels differ depending on type of nerve injury: decreased after CCI and partial nerve ligation, increased after complete nerve ligation, and no change after neuritis [93]. Elevated IL-10 levels have also been detected in the ventrolateral orbital cortex of the brain, signifying the involvement of the central nervous system in neuropathic pain [55]. Administration of exogenous IL-10 alleviates allodynia in animal models of CCI and paclitaxel-induced neuropathic pain [94,95]. Drugs such as calcineurin, uliastatin, plasmid DNA, and viral vector indirectly increase IL-10 concentrations [7,96,97], and may be promising therapeutic targets in the treatment of neuropathic pain.

3.3. TGF- β

Similar to IL-10, transforming growth factor beta (TGF- β) has been identified to affect neuropathic pain in different ways, depending on the anatomical location. Intrathecal administration of TGF- β reduces pain secondary to CCI and partial nerve ligation [98,99]. In contrast, injection of anti-TGF- β antibody into the red nucleus causes mechanical hypersensitivity in rats [100]. The underlying mechanism may be a tightening of the blood-spinal-cord-barrier (BSCB) against inflammatory molecules following nerve damage. In rats, it has been shown that TGF- β administration maintains elevated levels of tight junction proteins in the setting of nerve injury, thereby preserving the integrity of the BSCB [101]. Flexibilide, a substance derived from soft coral, has also been shown to alleviate neuropathic pain in rats via prevention of TGF- β decrease after CCI [102]. More recently, delivery of bone marrow stromal cell into the spinal cord of mice was used to induce TGF- β secretion, reducing CCI-induced neuropathic pain [103].

4. Alternative approaches to reduce neuroinflammation

Rather than targeting specific cytokines, other methods have been developed to modulate the immune system as a whole in the treatment of neuropathic pain. These approaches aim to reduce the amount of neuroinflammation following nerve injury, thereby producing an analgesic effect. Glucocorticoids, which broadly and nonspecifically suppress the immune response, are commonly used in clinical practice to alleviate neuropathic pain in conditions such as lumbar radiculopathy and to prevent inflammation following nerve damage, such as spinal cord injury [104,105]. They have also been found to prevent development of neuropathic pain [106], possibly through a decrease in TNF- α concentrations in mast cells [107]. However, despite a number of clinical trials for various conditions, the true clinical effectiveness of glucocorticoids for neuropathic pain remains unclear [108]. Given the complexity of the issue, a detailed discussion of it is beyond the scope of this review, but the ongoing debate explains the interest in alternative immunosuppressive therapies for neuropathic pain.

Novel immunomodulatory approaches being explored for neuropathic pain include ibudilast, hyperbaric oxygen, and botulinum toxin injection. Ibudilast is a phosphodiesterase inhibitor originally developed as an asthma medication. It crosses the blood-brain barrier, and has been found to decrease hindpaw hypersensitivity in both spinal cord injury (SCI) and CCI rats [109]. In other animal studies of neuropathic pain models, ibudilast has been found to suppress glial cell activation and reduce the production of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6) [110]. A recently published RCT found that an 8-week course of ibudilast was not effective for migraine, but there are no published studies of ibudilast for neuropathic pain conditions [111].

Hyperbaric oxygen therapy (HBOT) has been studied as a potential treatment for neuropathic pain. In rats following CCI, HBOT led to a decrease in allodynia. The treatment was associated with lower levels of TNF- α , suggesting a potential anti-inflammatory effect, but it did not affect levels of IL-1 β . The investigators proposed that HBOT increases the total oxygen content within the circulation, thereby supplying the increased need for oxygen in the damaged areas, which would reduce ischemic and reperfusion damage (and inflammation) that may result in pain [112].

Botulinum toxin (BoNT), the paralytic neurotoxin produced by the bacterium *Clostridium botulinum*, is currently prescribed for a variety of medical conditions, including muscle spasm, cervical dystonia, migraines, and hyperhidrosis, in addition to its well-known cosmetic uses. BoNT has been shown to attenuate pain via modification of neuroinflammatory activity induced by nerve damage [113]. In a rat model of neuropathic pain, botulinum toxin administration reduced pain-related behaviors, with corresponding downregulation of pro-inflammatory cytokines (IL-1 β and IL-18) and upregulation of anti-inflammatory cytokines (IL-10 and IL-1 receptor antagonist) [114]. The largest trial of BoNT for neuropathic pain is an unpublished study from Allergan (manufacturer of Botox[®]), which found a lack of efficacy of Botox[®] for the treatment of postherpetic neuralgia [115]. However, two recent clinical trials suggest that BoNT may prove to be beneficial in providing neuropathic pain relief. Han et al. studied 40 patients with SCI-

associated neuropathic pain and found that a one-time dose of subcutaneous BoNT provided at least 20% pain relief to 45% of patients at 8 weeks, compared to only 10% of patients in the placebo group [116]. Attal et al. found that two administrations of BoNT 12 weeks apart significantly reduced pain intensity over 24 weeks compared with placebo [117]. Patients with the best response to BoNT treatment were those who had increased brush allodynia and increased intra-epidermal nerve fiber density. The investigators suggested that BoNT may therefore be more effective for pain related to nociceptor sensitization, ectopic firing, and central sensitization (i.e., “irritable nociceptors”), which hints at a possible mechanism for BoNT-mediated analgesia in neuropathic pain conditions.

5. Conclusion

Neuropathic pain is a complex phenomenon caused by interactions between multiple physiologic systems, including the immune system. Based on the current evidence, both pro- and anti-inflammatory cytokines appear to play an important role in the development of neuropathic pain. Although there have been several intriguing preclinical studies suggesting specific cytokines as promising treatment targets for neuropathic pain, there have been very few clinical trials of immune modulators for neuropathic pain. Results from those studies have been mixed, and limited by small sample size and patient heterogeneity. Other approaches may include using a single agent to target multiple aspects of the immune pathway to treat neuropathic pain. As we improve our understanding of the various mechanistic underpinnings of neuropathic pain and the role of cytokines in its development, we may find even more opportunities to treat this difficult pain condition.

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HIGHLIGHTS

- Elevated pro-inflammatory cytokines are associated with neuropathic pain.
- Therapies to alter cytokines levels have shown promise as potential therapies.
- Indirect therapeutic options have been shown to modulate the immune landscape.
- Additional studies are needed to determine efficacy in neuropathic pain patients.

Table 1

Comparison of cytokine targets in treating neuropathic pain in animal models and their clinical correlates.

| Cytokine | Location of action | Animal model | Clinical trials for neuropathic pain | Clinical drugs |
|-------------------|-------------------------|---|---|---|
| Pro-inflammatory | | | | |
| TNF- α | Periphery | CCI ^a , DM ^b , Disc herniation | Sciatica, spinal stenosis, lumbosacral radiculopathy | Infliximab, etanercept, adalimumab, certolizumab pegol, golimumab |
| IL-1 β | Periphery, brain, spine | Knock-out mice, peripheral nerve injury | – | Canakinumab |
| IL-6 | Periphery, spine | CCI, peripheral nerve injury, knock-out mice | Disc herniation, chronic regional pain syndrome, Sciatica | Tocilizumab |
| IL-17 | Periphery | CCI, peripheral nerve injury, chemical injection, knock-out mice, arthritis | – | Secukinumab |
| Anti-inflammatory | | | | |
| IL-4 | Periphery | CCI, partial nerve injury | – | Glatiramer acetate |
| IL-10 | Periphery, brain | CCI, partial/complete nerve injury, neuritis | – | Calcineurin, uliastatin |
| TGF- β | Periphery, brain | CCI, partial nerve injury | – | Flexibilide |

^aCCI = chronic constriction injury.^bDM = diabetes mellitus.