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Topical review

Targeting cytokines for treatment of neuropathic pain

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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.

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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-1β, 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.

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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 down-regulation 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-1β, 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