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RECEIVED 16 July 2025

ACCEPTED 23 July 2025

PUBLISHED 07 August 2025

## CITATION

Mohsenin D, Yu J, Guan Z and Yu X (2025)  
Editorial: Microglia and tissue  
macrophages in pain.  
*Front. Immunol.* 16:1666972.  
doi: 10.3389/fimmu.2025.1666972

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# Editorial: Microglia and tissue macrophages in pain

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## KEYWORDS

microglia, macrophage, neuropathic pain, DRG, spinal cord, neuroinflammation

## Editorial on the Research Topic

### Microglia and tissue macrophages in pain

Following injury or diseases of the somatosensory nervous system, neuropathic pain is usually long-lasting and manifested with either negative symptoms such as loss of sensation or positive symptoms characterized by allodynia or hyperalgesia in a neuroanatomically plausible distribution (1). Neuropathic pain can be further divided into peripheral and central pathology. Common peripheral neuropathic pain includes trigeminal neuralgia, peripheral nerve injury-induced chronic neuropathic pain, postherpetic neuralgia, etc., whereas central neuropathic pain can coexist with lesions of the central nervous system such as traumatic brain and spinal cord injury, stroke and multiple sclerosis (MS) (2). With prevalence varying from 6.9% to 10% (3), neuropathic pain profoundly impacts human well-being, both physically and psychologically, with substantial health care costs. To date, managing neuropathic pain remains an unmet clinical challenge.

Over the past decades, there has been an exponential growth of both preclinical and clinical research on neuropathic pain. Insights of pain processing mechanisms have come from studying peripheral nerve injury induced neuropathic pain models (4), and neuroimmune interactions are increasingly recognized as an essential driver of neuropathic pain (5). It is well known that spinal microglia contribute to the induction and maintenance of neuropathic pain following peripheral nerve injury (6–9). Moreover, microglia also play a critical role in inducing sensitization of the dorsal horn pain processing circuitry by releasing pro-inflammatory mediators, such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and prostaglandin E2 (PGE<sub>2</sub>) (6). Notably, the contribution of microglia signaling to nerve-injury induced neuropathic pain is sexually dimorphic (10). Targeting spinal microglial cells to reduce injury-induced mechanical hypersensitivity is only effective in male mice and has little impact in female mice. On the other hand, a reciprocal interaction between sensory neurons and macrophages contributes to both acute (11) and persistent injury-induced neuropathic and inflammatory pain, in both sexes (12–14). A recent nociceptor-immune interactome study further predicts that macrophages are the strongest immune cell interactors of sensory neurons in the context of tissue injury (15).

Through preclinical studies, many potential analgesic targets implicated in neuropathic pain in rodents have been identified. Unfortunately, most molecular candidates have failed

to translate to the clinic. It has been increasingly debated among pain researchers and clinicians whether preclinical animal models reliably recapitulate human therapeutic responses, given interspecies biological differences (16, 17) and unreliable outcome measures (18).

In this Research Topic of *Frontiers in Immunology*, Dhir et al. set out to identify knowledge gaps in the research of investigating spinal microglia changes in murine models of neuropathic pain. Their comprehensive review found that changes in microglia and pain behavior were only acutely recorded up to 2 weeks after nerve injury in most of the 258 peer-reviewed articles. The findings highlight the need to study chronic pain models. Moreover, the authors call for the inclusion of both sexes in future chronic pain studies.

Aiming for developing novel nonopioid pain treatment, Ruan et al. focused on ozone therapy in chronic constriction injury of the sciatic nerve animals. The authors demonstrated that Ozone significantly alleviated neuropathic pain by promoting macrophage efferocytosis and suppressing neuroinflammation through the AMPK/Gas6-MerTK/SOCS3 signaling pathway. Although Ozone therapy has been proposed as an adjunct pain treatment for its antimicrobial, anti-inflammatory properties (19), its efficacy and long-term safety remains to be determined.

With etiology poorly understood, neuropathic pain commonly occurs in 20% to 50% of MS patients (20, 21). Ouyang et al. now explored the risk factors of neuropathic pain in MS. The authors concluded that the neuropathic pain risk parallels with the chronicity of spinal lesions in MS patients. Meanwhile, extended cervical and thoracic lesions were independent risk factors of neuropathic pain. The researchers further encouraged early attention to spinal cord lesions to improve pain management in patients with MS.

Chemotherapy-induced neuropathic pain (CINP) is also common among cancer patients. Moraes et al. investigated the role of spinal high-mobility group box 1 (HMGB1) in CINP. Their findings suggest that targeting the release of HMGB1 during the early stages of CINP may relieve neuropathic pain by reducing pro-inflammatory cytokines release from spinal microglia.

Taken together, this Research Topic aims to addressing the gaps in chronic pain research, emphasizing longitudinal studies and inclusive experimental designs. The findings further underscore the complementary roles of microglia and macrophages in the development and resolution of neuropathic pain. Integrating

insights from both compartments will hold promise for translating neuroimmune findings into the clinic and improving pain management.

## Author contributions

DM: Writing – original draft. JY: Writing – original draft. ZG: Writing – review & editing. XY: Writing – original draft, Conceptualization, Writing – review & editing, Supervision.

## Funding

The author(s) declare financial support was received for the research and/or publication of this article. Current work in Yu laboratory is supported by the Ongoing Project Award from the UCSF Department of Anesthesia and Perioperative Care, NIH R01AR081964 and NIH 3R01AR081964-02S1.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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