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Research Progress of Microglia Involved in Neuropathic Pain in Recent Ten Years ----Bibliometric Analysis Based on CiteSpace

Huang Xiong[1], Zhou Wei[2], Li Jun[*]

[1]School of Stomatology, Youjiang Medical University for Nationalities, Baise, Guangxi, China.
[2]School of Stomatology, Youjiang Medical University for Nationalities, Baise, Guangxi, China.
(Corresponding Author)[*]Department of Stomatology, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, Guangxi, China.
Email: Huang Xiong, 2426759260@qq.com; Zhou Wei, 215017175@qq.com; Li Jun, 2357396229@qq.com

Abstract: Based on CiteSpace, this study performed a bibliometric analysis of 400 articles (100 English, 300 Chinese) from PubMed and CNKI (2015–2025) to investigate the role of microglia in neuropathic pain (NP). The findings reveal a growing volume of literature in this field, with neuroinflammation representing a major research focus. Keyword analysis identified "neuroinflammation" (Chinese frequency: 62, centrality: 0.55) and "neuropathic pain" (English frequency: 60, centrality: 0.51) as the most representative terms. Microglia modulate inflammatory responses via M1/M2 polarization, involving channels such as TRPV4 and VRAC, and signaling pathways including CXCL13 and NLRP3, playing a central role in NP development. Future research should further elucidate microglial heterogeneity and immune regulatory mechanisms to identify novel therapeutic targets for NP.

Keywords: Microglia, Neuropathic Pain, Neuroinflammation, Microglia Polarization, Neuroinflammation Regulatory Pathways

Neuropathic pain (NP) is defined as pain resulting from lesions or diseases of the somatosensory system[1]. As a refractory pain syndrome, NP exerts long-term adverse effects on patients' diet, sleep, and general functioning, and may increase the risk of comorbid mental disorders such as anxiety and depression. Elucidating the pathogenesis and improving clinical management of NP remain major challenges and active areas of medical research. Microglia, a type of glial cell in the central nervous system (CNS), account for 10%–15% of all brain cells and constitute the most rapid and critical immune barrier in the CNS[2]. Studies indicate that as resident immune cells of the CNS, microglia play a significant role in the onset and progression of NP[3] Upon activation, microglia release cytokines and polarize into two primary phenotypes: the neurotoxic M1 type, which exerts pro-inflammatory and injurious effects, and the neuroprotective M2 type, which promotes repair and anti-inflammatory responses. These polarized states profoundly influence the immune milieu of the CNS. To outline advances over the past decade in understanding the role of microglia in NP, this review retrieved and screened relevant literature from the PubMed and CNKI databases, summarizes current research trends, and aims to provide a reference for future investigations in this field.

1 Literature sources and retrieval methods

Literature was retrieved from the PubMed database, developed by the National Center for Biotechnology Information (NCBI), and the China National Knowledge Infrastructure (CNKI) database. Search terms included "microglia" AND "neuropathic pain" for English literature and their Chinese equivalents for CNKI. The publication date was restricted to August 2015–August 2025. Following screening, 300 Chinese and 100 English articles closely related to the research focus were selected for analysis.The target literature was analyzed using CiteSpace (version 5.7.R2), a Java-based software for scientific mapping, to visualize collaboration networks and conduct co-occurrence analysis[4]. In the resulting networks, the node count reflects the number of countries/regions, authors, or keywords; edges denote relationships between nodes, with each edge indicating a collaboration or co-occurrence between two entities in the same publication; and network density—defined as the ratio of actual connections to all possible connections—quantifies the overall cohesion of the collaboration network.

2 Bibliometric analysis results

2.1 Annual distribution of literature

Between August 2015 and August 2025, a total of 400 publications (100 in English and 300 in Chinese) focusing on microglia and NP were identified and included in this analysis following the removal of duplicates and irrelevant records. The annual publication output in this field shows a consistent upward trend, reflecting its growing recognition among the research community. This pattern suggests that scientific interest in microglia and NP will continue to expand, attracting further investigation by domestic and international researchers in the coming years.

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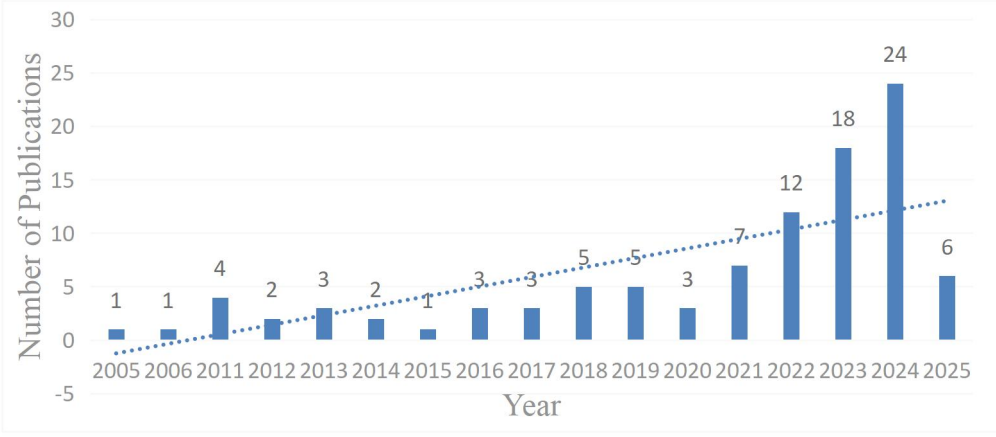

Fig. 1 Annual distribution of research literature on microglia and neuropathic pain（English）

Fig. 2 Annual distribution of research literature on microglia and neuropathic pain (Chinese)

2.2 Scientific research cooperation network analysis

Scientific research cooperation is that researchers work together to produce new scientific knowledge. Bibliometrics measures the scientific cooperation of researchers in this field by co-publishing papers.

2.2.1 Distribution and connection of paper source institutions

Distribution and collaboration among research institutions: A cooperative network analysis was performed on the affiliations associated with publications concerning microglia and NP over the past decade. Results indicate that research activity in this field is predominantly concentrated within the medical sector. Among international institutions, studies are largely centered in anesthesia pain management and pharmacology, whereas domestic institutions show a more even distribution across pharmacology-related neurology disciplines. This pattern suggests that domestic researchers emphasize how clinical drugs exert therapeutic effects on NP via microglial mechanisms, while international scholars focus more on the mechanisms and management of microglia-mediated pain in NP.

Table 1 Domestic ranking of publishing institutions of microglia and NP related research papers within retrieval time

Ranking	Institution	Documents Quantity
1	Inner Mongolia Medical University	5
2	Southern Medical University	4
3	Jilin University	4
4	Nanchang University	3
5	School of Acupuncture and Massage, Beijing University of Chinese Medicine	3
6	First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine	3
7	Chongqing Medical University	3
8	College of Integrated Traditional Chinese and Western Medicine, Fujian University of Traditional Chinese Medicine	3
9	Nanjing Medical University	3
10	College of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine	2

Table 2 Foreign ranking of publishing institutions of microglia and NP related research papers within retrieval time

Ranking	Institution	Documents Quantity
1	Department of Anesthesiology	20
2	Department of Molecular and System Pharmacology	9
3	Department of Neurology	7
4	Department of Physiology	7
5	Department of Life Innovation	6
6	College of Traditional Chinese Medicine	3
7	Alan Edwards Centre for Research on Pain	3
8	Department of Biochemistry and Molecular Biology	3
9	Department of Anesthesiology and Pain Medicine	3
10	Department of Neuroscience	3

2.2.2 Distribution of authors:

Cooperative network analysis of authors reveals a structure comprising 355 nodes and 679 links, with a network density of 0.0073. These metrics reflect limited collaboration between domestic and international authors, as nodes tend to form distinct clusters, often defined by institutional or regional affiliation. Collaboration is more frequent among researchers from the same institution, underscoring a need to foster broader scientific cooperation in this field. The leading contributors in terms of publication output in this area are listed below.

Table 3 Ranking of authors with high number of published papers on microglia and NP within the retrieval time

Ranking	Author	Author Units	Main Study	Documents Quantity
1	Tsuda, Makoto	Kyushu University	Microglia, P2X4 Receptor, BDNF, Neuropathic Pain	14
2	Inoue, Kazuhide	School of Pharmacy, Kyushu University	Purinergic signal, Neuroimmunity, Pain Pharmacology	10
3	Salter, Michael W	University of Toronto	Pain Synaptic Plasticity, NMDA Receptor, Microglia-neuron Interaction	5
4	Beggs, Simon	University of Toronto	Developmental Pain, Microglia, Epigenetics	5
5	Jing, Bei	College of Traditional Chinese Medicine, Jinan University	Microglia and astrocytes are involved in the mechanism of neuropathic pain	4
6	Fiore, Nathan T	University of Melbourne	Neuropathic pain and chemotherapy-induced peripheral neuropathy (CIPN), Neuroimmune Inflammation, Axonal Degeneration	3

2.3 Co-occurrence analysis

In the statistics of keywords in Chinese and English literature, the centrality of keywords indicates the frequency of being cited as article keywords in the selected literature. The keywords with the strongest centrality were neuropathic pain, spinal cord and microglia polarization; neuroinflammation, inflammation and polarization. The centralities are: 0.51, 0.36, 0.22; 0.55, 0.2, 0.13; among them, the most prominent in both Chinese and English literature is neuroinflammation.

Table 4 Keyword centrality of related research papers on microglia and NP (English)

Key Words	Frequency	Centrality (100%)
Neuropathic Pain	60	0.51
Spinal Cord	11	0.36
Microglia Polarization	5	0.22
Spinal Cord Injury	5	0.17
Proinflammatory Cytokines	3	0
Chronic Pain	3	0.05
Sex Differences	2	0
Peripheral Nerve Injury	2	0
Spared Nerve Injury	2	0.15
Trigeminal Neuropathic Pain	2	0

Table 5 Keyword centrality of related research papers on microglia and NP (Chinese)

Key Words	Frequency	Centrality (100%)
Neuroinflammation	62	0.55
Inflammation	24	0.2
Polarization	18	0.13
Lipopolysaccharide	17	0.18
Electroacupuncture	16	0.24
Inflammatory Reaction	14	0.05
Depression	13	0.14
Parkinson Disease	12	0.06
Spinal Cord Injury	12	0.14
White Rat	9	0.12

3 Research progress on the relationship between microglia-mediated neuroinflammation and NP

3.1 Microglia phenotype and neuroinflammation

Co-occurrence analysis indicates that research on the role of microglia in NP primarily centers on neuroinflammation, which is closely linked to their activation state. According to literature analysis [5] , [6] , resting microglia can be classified into two morphological forms: (1) branched morphology, characterized by an oval cell body with fine, extending processes; and (2) intermediate morphology, featuring an elongated cell body with reduced branching. Upon exposure to harmful stimuli such as infection or trauma, microglia transition into an activated state, displaying fewer branches, an irregular cell body, and a darker-stained amoeboid appearance[7] . This activation leads to diverse functional phenotypes—a process termed microglial polarization[8] . Resting (M0) microglia undergo a series of morphological and functional changes upon activation, ultimately polarizing into the pro-inflammatory (M1) phenotype or the anti-inflammatory (M2) phenotype[9] . M1 microglia release pro-inflammatory factors and harmful mediators that aggravate inflammatory cell infiltration, whereas M2 microglia alleviate the inflammatory response by secreting anti-inflammatory factors. Acute and controlled activation of microglia confers neuroprotective benefits and promotes neural repair; however, sustained activation often results in the excessive release of neurotoxic pro-inflammatory (M1) cytokines and other inflammatory mediators[9] . Lipopolysaccharide (LPS) promotes M1 polarization, leading to the secretion of interleukin (IL)-12, tumor necrosis factor-α (TNF-α), and IL-1β, which upregulate inducible nitric oxide synthase (iNOS) and surface markers CD68 and CD86. Conversely, IL-4 and IL-10 induce M2 polarization and the production of anti-inflammatory factors, thereby exerting neuroprotective effects[10] , [11] , [12] . Studies indicate that ACT001 suppresses AKT phosphorylation, thereby inhibiting NF-κB nuclear translocation in microglia, which reduces NLRP3 inflammasome secretion from M2-type microglia and attenuates neuroinflammatory responses[13] , Similarly, low-intensity pulsed ultrasound has been shown to downregulate M1 markers CD86 and CD68 while enhancing M2-related markers Arginase-1 (Arg-1) and IL-10, thereby mitigating microglial pro-inflammatory activity[11] . Collectively, these findings demonstrate that microglia predominantly polarize toward the M1 phenotype, generating pro-inflammatory factors that drive neuroinflammation and contribute to neuropathic pain.

3.2 Microglia regulate neuroinflammation involved in NP

3.2.1 Activation mechanism of microglia and its core role in neuroinflammation

As the primary immune cells of the central nervous system (CNS), microglia play a pivotal role in neuroinflammation. Following nerve injury or lesion, microglia undergo rapid activation and proliferation, accompanied by significant morphological and functional alterations. These changes include the amplification of inflammatory cascades through the release of pro-inflammatory factors[4] . This activation process, governed by diverse molecular signaling pathways, represents an initiating event in the development of neuropathic pain.

Role of the TRPV4 channel: The transient receptor potential vanilloid type 4 (TRPV4) channel is expressed in microglia and represents a key mediator of their activation. In models of nerve injury, either genetic knockout or pharmacological blockade of TRPV4 significantly alleviated neuropathic pain-like behaviors, such as mechanical allodynia. Mechanistically, microglial TRPV4 promotes its own activation and proliferation, and—through the release of lipocalin-2—enhances functional and structural plasticity of spinal excitatory neurons, thereby converting peripheral nerve injury into central sensitization. These findings position microglial TRPV4 at the core of the spinal neuroimmune axis, identifying it as a critical hub for neuroinflammation and pain transmission[14] .

VRAC channels and ATP release: The volume-regulated anion channel (VRAC) represents another key mechanism through which microglia regulate neuroinflammation. Swell1 (*Lrrc8a*), an essential subunit of VRAC, plays a central role in mediating ATP release. In mice with microglia-specific Swell1 deficiency, nerve injury-induced increases in extracellular ATP in the spinal cord were significantly attenuated, accompanied by reduced microglial proliferation, decreased neuronal activity in the spinal dorsal horn, and alleviation of neuropathic pain-like behaviors. Further drug screening identified the FDA-approved compound dicumarol as a VRAC inhibitor; its intrathecal administration alleviated nerve injury-induced mechanical allodynia in mice. These findings demonstrate that VRAC-mediated ATP release is a determinant in spinal neuropathic pain and a potential therapeutic target[15] .

The unique role of CD11c microglia: Following nerve injury, a subset of microglia expressing CD11c emerges during behavioral pain hypersensitivity and participates in both pain recovery and recurrence. Depletion of $CD11c^{+}$ microglia prevents spontaneous recovery from pain hypersensitivity in mice. These cells express insulin-like growth factor-1

(IGF1), and disruption of IGF1 signaling reproduces this impaired pain recovery phenotype. Moreover, ablating $CD11c^+$ microglia or blocking IGF1 signaling during the recovery phase leads to pain relapse, demonstrating the protective role of IGF1 in microglia-mediated neuroinflammation and revealing a novel mechanism underlying pain resolution[16].

These activation mechanisms highlight microglia as the "master regulator" of neuroinflammation, which directly drives the neuroinflammation cascade by regulating the release of key ion channels and factors.

3.2.2 Molecular signaling pathways of microglia-regulated neuroinflammation in the development of pain

Neuroinflammation involves a complex process of cell-cell interaction and signal amplification. Microglia regulate the occurrence and development of pain by releasing inflammatory mediators. Neuroinflammation not only promotes neurosensitization, but also mediates the persistence and recurrence of pain.

Chemokine and cytokine pathways: The microglia-regulated chemokine CXCL13 plays a key role in neuropathic pain. Downregulation of ZNF382 is a prerequisite for pain development, mediated through the release of a distal cis-acting silencer on the Cxcl13 promoter, thereby driving CXCL13 expression[9]. CXCL13 activates its receptor CXCR5, leading to neuronal sensitization; in animal models, mimicking ZNF382 downregulation induces pain-like behavior, whereas CXCL13 knockdown or CXCR5 knockout alleviates pain[17]. Furthermore, members of the transforming growth factor-β (TGF-β) superfamily, such as follistatin, modulate cytokine activities in neuroinflammation and contribute to pain pathogenesis [18]. These pathways illustrate how microglia amplify inflammatory signals via transcriptional regulation.

Cell death and inflammasome pathways: Neuroinflammation involves multiple cell death pathways, including intrinsic apoptosis, extrinsic apoptosis, autophagy, ferroptosis, pyroptosis, and necrosis, all of which contribute to the inflammatory response in neuropathic pain. Microglia express NLRP3 inflammasome-forming proteins—such as ASC and caspase-1—and regulate inflammasome activity. Small molecule compounds targeting these cell death pathways have been shown to alleviate pain in preclinical models, indicating that microglia-mediated inflammation sustains pain states by inducing death of neuronal and glial cells [19], [20].

Immune cell interactions: Microglia cooperate with other immune cells to amplify neuroinflammation. For instance, B cells contribute to neuropathic pain development by secreting IgG, which interacts with Fcγ receptors (FcγRs) expressed on sensory neurons, microglia, and macrophages, forming immune complexes that drive mechanical allodynia and sensory neuron hyperexcitability [13]. This pro-nociceptive effect was abolished in FcγR-deficient mice with nerve injury, confirming the essential role of the B cell–IgG–FcγR axis in pain pathogenesis [21]. Additionally, IL-10 derived from non-microglial sources—such as natural killer cells and neutrophils—modulates microglial activity to prevent excessive activation, highlighting the dual role of the immune system in inflammation regulation: it not only promotes inflammation but also delivers anti-inflammatory signals that facilitate pain recovery [21].

These molecular pathways indicate that microglia, as the hub of neuroinflammation, integrate peripheral injury signals through multi-signal cascades, leading to central nervous system sensitization and chronic pain.

4 Summary and outlook

Over the past decade, the volume of publications on microglia and NP has shown a consistent upward trend, with 400 Chinese and English articles included in this analysis. Keyword centrality analysis highlights neuroinflammation as a major research focus, indicating strong scholarly interest in the role of microglia in neuroinflammation, central sensitization, and pain progression. As the first immune cells activated and recruited to inflammatory sites, microglia exert both neuroprotective and neurotoxic effects. Microglia-mediated neuroinflammation is considered a key factor in the development of NP, though its precise role in NP pathogenesis and treatment remains debated. Elucidating how microglia contribute to NP not only advances our understanding of its cellular and molecular mechanisms but also offers new insights and potential targets for therapeutic and early interventions. Bibliometric analysis underscores the importance of further investigating how microglia regulate neuroinflammation in NP. Future studies should focus on the dynamic functions of microglial heterogeneity in pain and explore immune-mediated analgesic mechanisms to develop more effective interventions for neuropathic pain.

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