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REVIEW

Microglia Polarization: A Key Regulatory Mechanism of Neuropathic Pain

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Abstract: Neuropathic pain is a chronic pain syndrome resulting from damage or dysfunction to the somatosensory nervous system, significantly impairing patients' quality of life. Microglia play a crucial role in the development and maintenance of neuropathic pain, particularly through their polarization mechanisms. This review summarizes the regulatory mechanisms underlying microglial polarization in neuropathic pain, the associated signaling pathways, pharmacological agents that modulate microglial polarization, and intervention strategies targeting neuropathic pain. We emphasize the intrinsic link between microglial polarization and neuropathic pain, aiming to identify potential therapeutic targets and provide a scientific basis for drug development and preclinical research in the treatment of neuropathic pain.

Keywords: neuropathic pain, microglia, polarization

Introduction

Neuropathic pain (NP) is a chronic pain syndrome resulting from damage or dysfunction of the somatosensory nervous system, characterized by spontaneous pain, hyperalgesia, and allodynia.[1] The global prevalence of NP ranges from 7% to 10%, with common causes including traumatic nerve injury, diabetic neuropathy, and viral nerve invasion.[2] NP is frequently accompanied by mental health disorders such as insomnia, anxiety, and depression, which significantly impair patients' quality of life and overall well-being, thereby imposing a substantial economic burden on society.[2] Current treatment modalities, such as gabapentinoids and opioids, primarily target neuronal mechanisms to produce analgesia; however, their clinical utility is limited by suboptimal efficacy, poor tolerability, and notable adverse effects.[3] Therefore, there is an urgent need to investigate novel pathophysiological mechanisms and identify potential therapeutic targets.

Microglia are resident immune cells in the central nervous system (CNS), constituting approximately 10% of the total CNS cells population, and play a core role in maintaining neural homeostasis and modulating inflammatory responses.[4] Under physiological conditions, microglia remain in a quiescent state, however, upon exposure to injury or inflammatory stimuli, they rapidly become activated and undergo morphological and functional transformations, a process known as polarization. Upon activation, microglia can polarize into either a pro-inflammatory M1 type, which secretes pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β, or an anti-inflammatory M2 type, which releases anti-inflammatory mediators such as IL-10 and transforming growth factor-β (TGF-β), thereby dynamically regulating the neuroinflammatory response. Accumulating evidence suggests that microglial polarization critically influences the initiation and progression of NP. In NP models, enhanced M1 polarization of microglia in regions such as the spinal dorsal horn and prefrontal cortex triggers neuroinflammatory cascades and disrupts synaptic plasticity,

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whereas promoting M2 polarization alleviates pain symptoms and facilitates nerve repair.[5,6] Therefore, targeted modulation of microglial polarization represents a promising therapeutic strategy for NP.

However, studies have indicated that microglial involvement in disease states cannot be simply categorized by the M1/M2 dichotomy; instead, they exhibit a spectrum of intermediate transitional states. Scholars have identified a novel microglial subtype, termed disease-associated microglia (DAM), initially discovered in Alzheimer's disease research.[7] DAM represents a distinct subpopulation activated beyond the homeostatic state. The DAM concept provides a theoretical framework and research paradigm for identifying analogous "pain-associated microglia" in neuropathic pain. This review outlines the involvement of microglial polarization in NP, discusses the signaling pathways that regulate this process, and explores potential interventions targeting microglial polarization, aiming to provide a theoretical foundation for a deeper understanding of NP pathogenesis and the development of immune microenvironment-targeted therapeutic strategies.

The Role of Microglia in the CNS

Microglia originate from macrophage progenitor cells derived from the embryonic yolk sac and migrate into the CNS before the establishment of the blood-brain barrier during early embryonic development.[8] As the primary resident immune cells of the CNS, microglia serve as a critical defense line and play an essential role in maintaining CNS homeostasis and neural function. During early CNS development, microglia regulate neuronal proliferation and differentiation through the secretion of neurotrophic factors such as brain-derived neurotrophic factor (BDNF).[9] During the process of neural development, microglia recognize and phagocytose redundant or incorrectly synapses, thereby ensuring the precise development and functional integrity of neural networks.[4] Additionally, Microglia can efficiently phagocytose neurons and other cells that undergo programmed death during development, preventing the accumulation of apoptotic cells and trigger inflammatory response, thus preserving the internal stability of the CNS.[10] Upon CNS injury, microglia rapidly initiate phagocytosis to remove harmful substances such as cell debris, protein aggregates and invading microorganisms, thereby limiting their spread within the CNS.[11] Meanwhile, microglia migrate swiftly to the injury site and contribute to glial scars formation by secreting extracellular matrix components and growth factors, which provide structural support for tissue repair.[12] In parallel, microglia secrete a variety of neurotrophic factors, promoting the survival, repair and regeneration of neurons, and enhancing the resistance of neurons to damage.[13] Collectively, microglia exert a crucial regulatory role in neural development, synaptic pruning, immune surveillance, and the repair of neural injuries.

Microglial Activation and Polarization

Under normal physiological conditions, microglia remain in a quiescent state and exhibit a ramified morphology. Microglia constantly swing their slender surface protrusions to interact with neurons, astrocytes and blood vessels, detect the functional status of synapses, thereby monitoring changes in the microenvironment and maintaining the homeostasis of the CNS.[14] Conversely, under pathological conditions, microglia rapidly become activated, proliferate and migrate toward the site of injury. This activation results in an enlarged cell body, shortened processes, and a morphological transformation from a ramified to an amoeboid form.[15] Microglia can adopt distinct phenotypes according to stimulation, environment and period, which is called microglial polarization. Similar to macrophages, microglial polarization is categorized into classically activated (M1) and alternatively activated (M2).

The classically activated phenotype, commonly referred to as the M1 type, is mainly induced by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), including lipopolysaccharide (LPS), TNF-α and interferon-γ (IFN-γ).[16] M1-type microglia exhibit a pro-inflammatory profile and are capable of secreting a wide range of pro-inflammatory mediators, such as IL-1β, IL-6, TNF-α, NADPH oxidase (NOX), inducible nitric oxide synthase (iNOS), major histocompatibility complex class II (MHC-II), chemokine C-C motif ligand 2 (CCL2), chemokine C-X-C motif ligand (CXCL) 9, CXCL10, nitric oxide (NO), and reactive oxygen species (ROS).[17] M1-type microglial activation is typically associated with acute inflammatory responses and contributes to the clearance of pathogens and damaged tissues by enhancing phagocytosis. However, as the population of M1 microglia increases, phagocytosis markedly declines, while the production of inflammatory cytokines, chemokines, and other neurotoxic

mediators increases, thereby amplifying inflammatory processes and exerting neurotoxic effects.[18] The activation of M1-type microglia can be assessed by evaluating the expression of specific surface markers, including CD11b, CD16, CD32 and CD86. Nevertheless, since macrophages can also express these markers, detecting these markers cannot distinguish microglia from macrophages. Some researchers propose using transmembrane protein 119 (TMEM119) as a marker of resting microglia in the CNS to distinguish it from peripherally derived macrophages.[19] However, in disease states, studies have shown that the expression of TMEM119 in activated microglia decreases instead, and TMEM119 is non-specifically expressed in dendritic cells,[20] indicating that the reliability of TMEM119 as a microglia-specific molecule is insufficient. Therefore, the accurate differentiation of activated microglia from infiltrating macrophages within the CNS remains a significant challenge.

The alternatively activated phenotype of microglia, also known as the M2 type, is induced by IL-4, IL-10 and IL-13, and is involved in inflammation suppression, tissue remodeling, angiogenesis and immune regulation. The M2 phenotype can be further divided into three subtypes: M2a, M2b, and M2c. Upon stimulation of IL-4 and IL-13, M2a microglia produce anti-inflammatory factors such as IL-10 and insulin-like growth factor-1 (IGF-1), increase the expression of arginase-1 (Arg-1), chitinase-like protein 3 (Ym1), and CD206, inhibit nuclear factor-κB (NF-κB) signal transduction and subsequent M1-type activation, and enhance phagocytosis.[21] Under the stimulation of immune complexes, crystallizable fragment-γ (Fc-γ) receptors and Toll-like receptors (TLRs), the M2b phenotype increases the expression of IL-1β, CD86, suppressor of cytokine signaling 3 (SOCS3), IL-6 and IL-10, and participates in phagocytosis and clearance of tissue debris.[22] The M2b subtype is considered an intermediate activation state, displaying features of both M1 and M2 phenotypes, and may function as a regulatory subtype within the M2 spectrum.[23] When the inflammatory response subsides, IL-10 and glucocorticoids can induce M2c polarization, up-regulate the expression of TGF-β, and participate in post-inflammatory tissue remodeling and matrix deposition.[24]

The dichotomous concept of microglial phenotypic polarization (M1/M2) originated from classic studies on the immune regulatory mechanisms of macrophages. However, recent advances in single-cell transcriptomic have revealed the unique biological characteristics of resident macrophages in the CNS. Through single-cell sequencing technology, researchers have identified that microglia exhibit at least nine distinct transcriptional states across embryonic development, aging, and brain injury, with their distribution demonstrating significant brain region specificity and life stage dependence.[25] Furthermore, microglia activation is not characterized by a binary opposition but exists along a continuous spectrum that encompasses various intermediate states, reflecting the dynamic and context-dependent response of these cells to environmental cues. Pro-inflammatory and anti-inflammatory are merely two extreme types of microglia classified based on their functions. Utilizing single-cell RNA sequencing technology, Li et al not only identified multiple microglial subpopulations in the chronic constriction injury (CCI) model but also delineated their dynamic transitional trajectories from homeostasis to distinct activated states through pseudotime analysis. The study revealed an "intermediate state" cell population existing between homeostatic and fully activated microglia, which may determine the ultimate fate of these cells and functionally interact with neuropathic pain (NP) progression.[26] Although the M1/M2 dichotomy is an oversimplification, this classification still helps to understand the functions of microglia in various CNS diseases. This phenotypic transition between these states allows microglia to both initiate and resolve neuroinflammatory responses, protect neural tissue, and maintain CNS homeostasis.

Imbalance of Microglial Polarization in NP

NP can be classified into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain, depending on the location of the injury within the peripheral or central nervous system. Commonly used animal models in NP research include central nervous system models such as spinal cord injury (SCI), as well as peripheral nerve models such as CCI of the sciatic nerve, spinal nerve ligation (SNL), spared nerve injury (SNI), diabetic peripheral neuropathic pain (DPNP), and chemotherapy-induced neuropathic pain (CINP), etc. These animal models provide a robust experimental basis for investigating the role of microglial polarization in NP. In all the aforementioned NP models, an imbalance in the M1/M2 polarization of spinal microglia was observed, which is closely associated with central sensitization and the progression of NP (see Figure 1).

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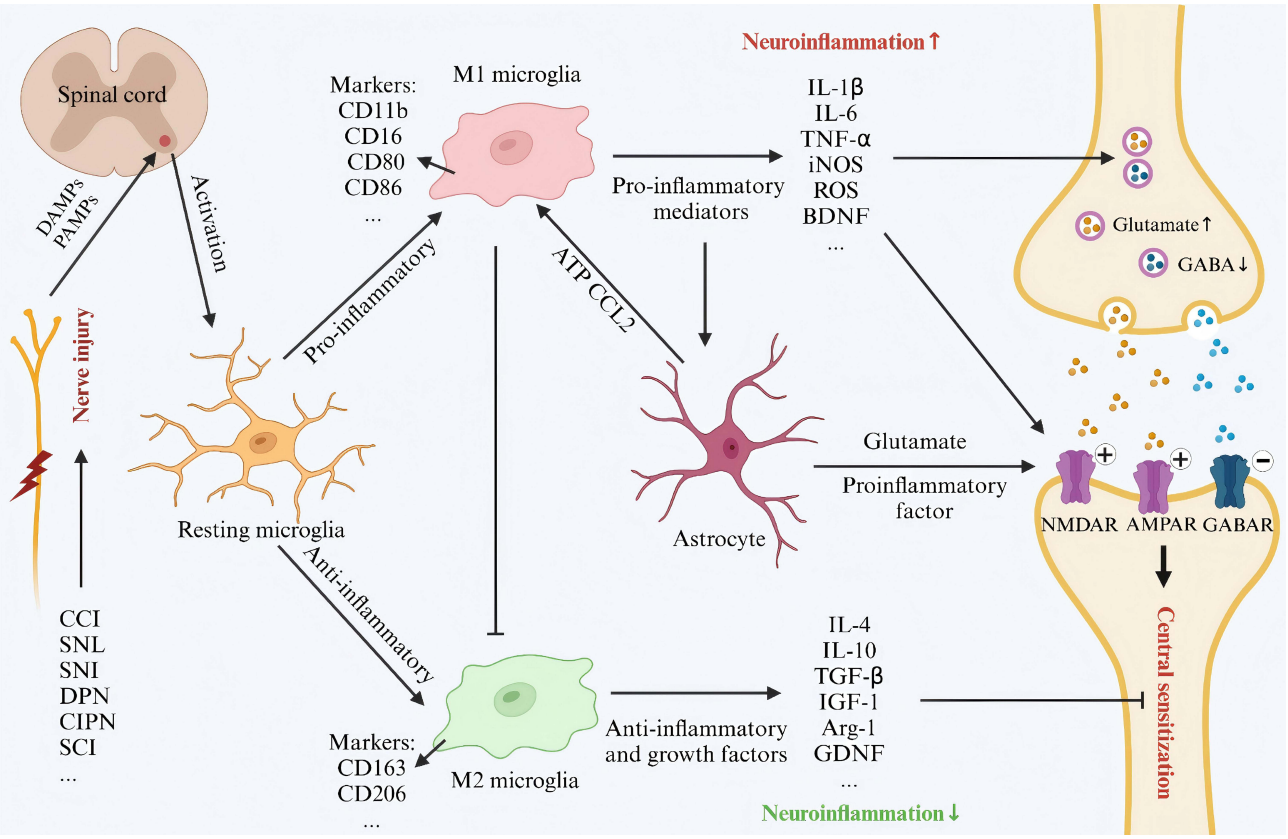

Figure 1 Imbalance of microglial polarization in the spinal cord promotes the development of NP. Black arrows indicate the direct targeting or action, red arrows represent upregulation, and green arrows denote downregulation.

Jin[27] reported that in the diabetic neuropathic pain (DNP) model, microglia in the rat spinal cord significantly polarized towards the M1 type, as evidenced by the significant increase in mRNA and protein levels of M1 markers (CD86, CD68, TNF-α, IL-1β), while M2 polarization was not significantly activated during the experimental time frame, suggesting that the neuroinflammation in DNP is mainly driven by M1-type microglia. On the 7th day after SNI model surgery, the activation of microglia in the spinal dorsal horn reached its peak and rapidly polarized towards the M1 type, while the M2 type polarization decreased.[28,29] An elevated M1/M2 ratio contributes to the intensification of neuroinflammation and is associated with the progression of NP. In the SCI model, microglia in the rat ventral posterolateral (VPL), ventral tegmental area (VTA), and periaqueductal gray (PAG) regions were found to exhibit an M1 type during the acute pain phase. As the condition progressed to the chronic phase, a significant increase in M2 type microglia was observed.[30] During the acute phase of NP, microglial polarization is predominantly characterized by the M1 type. However, this profile dynamically shifts toward the M2 type over time or in response to therapeutic interventions.

It is important to note that during the NP period, the polarization state of microglia is not constant but undergoes a dynamic regulation as the disease progresses. In the CCI model, on the first day after CCI surgery, spinal microglia transition from a resting state to an activated state, and M1/M2 phenotype related genes are upregulated; By the 7th and 14th day post-surgery, the number of microglia increased significantly, and their morphology was fully activated. At this stage, only M1 type marker genes remained highly expressed, while M2 type related genes were downregulated to baseline levels, indicating a shift towards pro-inflammatory M1 type in the late stage of microglia polarization.[31] This dynamic change suggests that the early co-activation of M1 and M2 may be involved in the acute response to nerve injury, whereas sustained M1 polarization becomes a key driver of the neuroinflammatory cascade and the progression of chronic pain.

The above research indicates that neural injury can rapidly induce microglia activation toward the M1 type, while simultaneously triggering an immediate protective M2 type response. However, as the injury signal persists, M1

polarization gradually becomes dominant and suppresses the function activity of the M2 type. It is noteworthy that the polarization pattern of microglia may also be related to age factors. Contrary to the M1-type microglial polarization observed in the spinal cord of adult rats after SNI, in the case of nerve injury in young rats, the polarization of microglia shifted to the M2 type and no hyperalgesia occurred in young rats; as young rats developed into adolescence, microglial polarization turned to the M1 type, accompanied by the appearance of NP symptoms.[32] In summary, microglial polarization undergoes dynamic changes following nerve injury, characterized by an initial co-activation of both M1 and M2 types, followed by a shift toward chronic M1 dominance. This transformation is closely linked to neuroinflammatory processes and the development of chronic pain. Based on this, precisely regulating the polarization balance of microglia, especially by inhibiting M1 polarization or promoting M2 activation, may be an effective strategy for intervening in the progression of NP.

Regulatory Mechanism of Microglial Polarization on NP Signal Transmission

Regulating Inflammatory Responses

The large amount of pro-inflammatory factors secreted by M1-type microglia is an important factor in exacerbating neuroinflammation and pain. After IL-1β, TNF-α and IL-6 bind to the corresponding cytokine receptors on neurons, they activate downstream signaling pathways such as NF-κB and mitogen-activated protein kinase (MAPK), leading to the activation of voltage-gated sodium channels and transient receptor potential channels on neurons, which alters the membrane potential of neurons and promotes the transmission of pain signals.[33] The NF-κB and MAPK signaling pathways further enhance the release of additional inflammatory mediators, thereby propagating an inflammatory cascade. In addition, the NO and ROS released by M1-type microglia can cause oxidative damage to neurons and glial cells, disrupt the integrity of nerve cell membranes, and further exacerbate neuroinflammation and pain. In contrast, anti-inflammatory cytokines such as IL-10 and TGF-β secreted by M2-type microglia exert protective effects by counteracting these processes.[24,34]

Regulation of Synaptic Plasticity

M1-type microglia impair synaptic structure and function by releasing inflammatory factors and neurotoxic substances, resulting in abnormal synaptic plasticity. Inflammatory mediators such as IL-1β, IL-6, TNF-α, PGE2 and CCL2 can promote the release of glutamate from presynaptic terminals and enhance the function of N-methyl-D-aspartate receptors (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) on postsynaptic membranes, thereby increasing excitatory synaptic transmission in neurons; Simultaneously inhibiting the release of γ-aminobutyric acid (GABA) from the presynaptic terminal and the functions of GABA receptors (GABAR) and glycine receptors (GlyR) on the postsynaptic membrane leads to a reduction in inhibitory synaptic transmission.[35] TNF-α, IL-1β and IL-6 also induce the phosphorylation of the transcription factor cAMP response element binding protein (CREB), which drives CREB-mediated transcription of pro-nociceptive genes (such as cyclooxygenase-2, neurokinin-1) in spinal neurons, thereby inducing long-term neuronal plasticity in the pain circuit.[35]

Crosstalk with Astrocytes

After nerve injury, microglia in the spinal cord are rapidly activated and activate astrocytes by releasing TNF-α.[36] Once activated, astrocytes secrete chemokines (CCL2 and CXCL1), inflammatory factors (TNF-α, IL-1β and IL-6), and glutamate, which directly act on neurons to enhance the transmission of pain signals.[37] Glutamate transporters such as GLT-1 and GLAST are expressed in astrocytes and regulate the clearance of glutamate from the synaptic cleft and extracellular space. After astrocytes activation, the activity of GLT-1 and GLAST is suppressed, leading to the accumulation of glutamate within the synaptic cleft and overactivation of NMDAR, triggering central sensitization.[38] In addition, D-serine released by astrocytes enhances synaptic transmission efficacy by interacting with the NR2B subunit of neurons.[39] Astrocytes simultaneously release ATP and CCL2, which further promote microglial polarization towards the M1 type and the release of inflammatory factors.[37] Therefore, the crosstalk between microglia and astrocytes

amplifies the inflammatory response and enhances neuronal excitability, forming a positive feedback loop that ultimately leads to the chronic development of NP.

Regulation Mechanism of Microglial Polarization in NP

Microglial polarization-mediated neuroinflammation represents a central pathological mechanism in NP and is regulated by multiple signaling pathways, such as the NF-κB pathway, TLRs pathway, and MAPK pathway, etc. Elucidating how these pathways regulate microglial polarization and interact with each other is crucial for understanding the molecular mechanisms underlying the onset and progression of NP. Furthermore, it provides potential therapeutic targets for drug development. This review summarizes several classic and key signaling pathways involved in the regulation of microglial polarization under NP conditions (see Figure 2).

NF-κB Pathway

The NF-κB signaling pathway plays a pivotal role in microglial polarization and NP. Under normal circumstances, NF-κB remains sequestered in the cytoplasm in an inactive form by binding to the inhibitory protein IκB. After peripheral nerve injury, primary sensory neurons release PAMPs or DAMPs to activate TLRs on the surface of microglia, which then activate IκB kinase (IKK) through proteins such as myeloid differentiation factor 88 (MyD88). IKK phosphorylates IκB, leading to its degradation and the release of NF-κB dimers. These dimers subsequently translocate into the nucleus, where they bind to κB response elements in the promoter regions of target genes and initiate the transcription of various pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6.[40] These pro-inflammatory factors prompt microglia to polarize towards the M1 type, triggering intense neuroinflammation and exacerbating NP symptoms. Accumulating

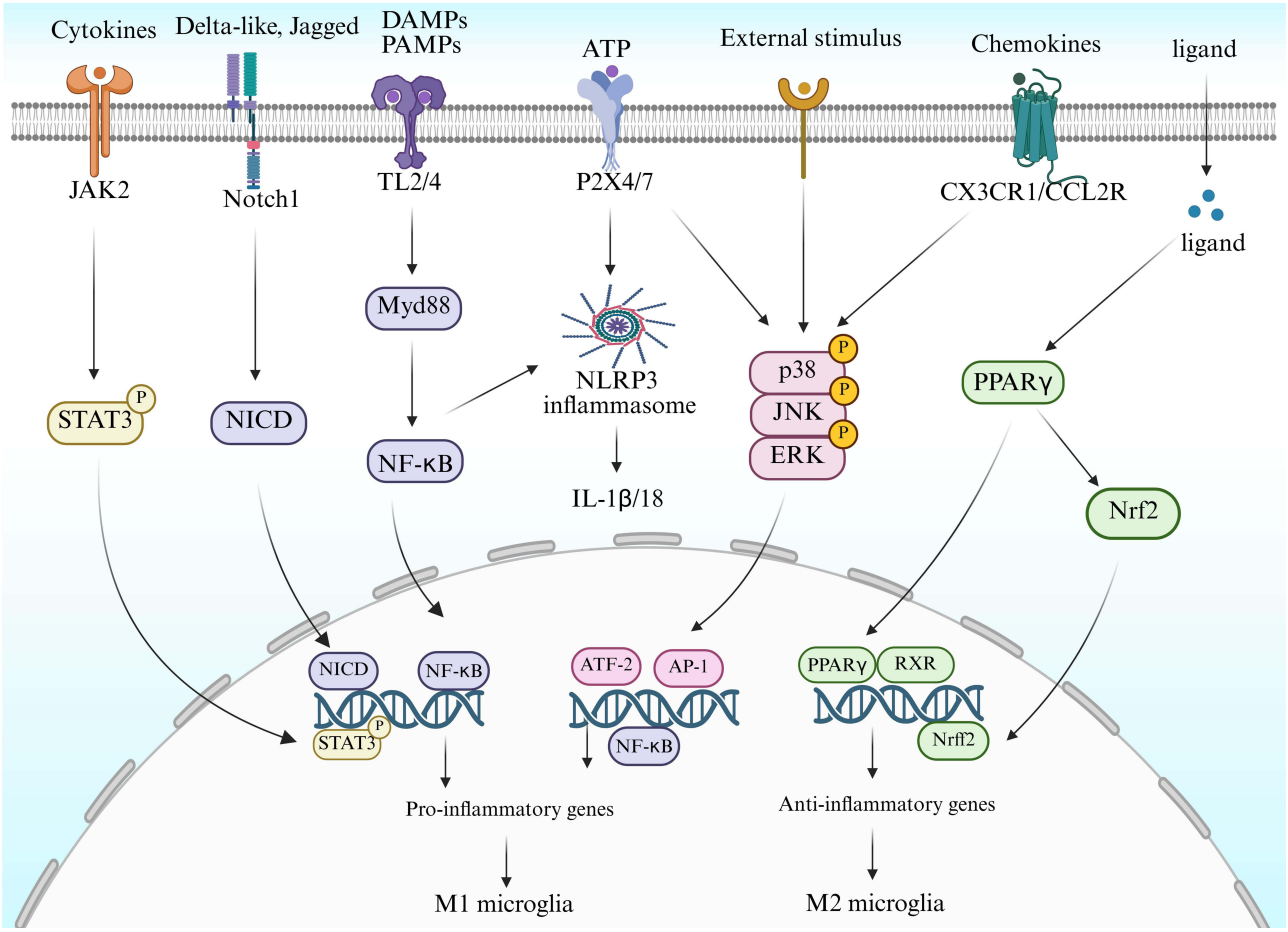

Figure 2 Signaling pathways regulating microglial polarization.

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evidence indicates that suppressing NF-κB pathway activation, along with its downstream effects on M1 microglial polarization and pro-inflammatory cytokine production, represents a promising therapeutic strategy for managing NP.[41]

MAPK Signaling Pathway

The MAPK signaling pathway family, which includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38MAPK, plays a complex regulatory role in microglial polarization and NP progression. When microglia are stimulated by neuroinjury-related factors such as cytokines, growth factors, and oxidative stress, they activate corresponding receptors and, through a series of adaptor proteins and enzyme cascades, activate MAPK.[42] Once activated, p38MAPK can phosphorylate various transcription factors including NF-κB and activating transcription factor 2 (ATF-2), upregulating the transcription of pro-inflammatory factor genes, and promote the polarization of microglia towards the M1 type.[43,44] JNK activation also contributes to the pro-inflammatory response by enhancing the activity of activator protein-1 (AP-1) through phosphorylation of c-Jun, which induces the expression of inflammatory mediators and further supports M1 polarization.[44] ERK has a bidirectional regulatory effect on microglial polarization under different stimuli and cellular environments. Moderate activation may promote M2 polarization and exert neuroprotective effects,[45] but excessive or abnormal activation may also cooperate with other pathways to promote M1 polarization and inflammation.[46] In NP, the MAPK signaling pathway is generally hyperactivated, resulting in an imbalance in microglial polarization and a shift toward the M1 type.[42]

TLRs Signaling Pathway

The TLRs signaling pathway serves as a critical mechanism by which microglia detect external stimuli, initiate immune responses and regulate polarization. TLRs are broadly distributed on the surface of microglia, with TLR2 and TLR4 being particularly implicated in the pathogenesis of NP.[37] Primary neurons release a variety of endogenous damage ligands that specifically bind to TLR2/4, such as LPS and high mobility group box 1 (HMGB1), after nerve injury. After binding to the ligand, TLR4 undergoes a conformational change, recruiting MyD88 to its intracellular segment to form a MyD88-dependent signaling complex, which leads to the rapid phosphorylation of IκB and subsequent dissociation of NF-κB, allowing it to enter the nucleus.[47] In addition, TLR2/4 can also activate members of the MAPK family, promoting the transcription of inflammatory factors and the M1 polarization of microglia.[47] Under the NP state, the expression of TLR2/4 increases, driving microglia to polarize towards the pro-inflammatory M1 type, exacerbating neuroinflammation and pain. However, knocking out TLR2/4 can alleviate the NP symptoms induced by nerve injury.[48]

Purinergic Receptor Signaling Pathway

Purinergic receptors, including P1 receptors and P2 receptors, are activated by binding with adenosine and adenosine triphosphate (ATP) and its analogues (ADP), respectively, and play a key role in microglial polarization and NP. Microglia express a variety of P2 receptors, among which P2X4 and P2X7 receptors mainly participate in the regulation of microglia by NP.[37] During the process of NP induced by nerve injury, the extracellular ATP level significantly increases, and the expression of P2X4R and P2X7R in microglia within the spinal dorsal horn is upregulated. After ATP binds to the P2X4 receptor, it causes an increase in intracellular calcium ion concentration in microglia, activates the downstream MAPK signaling pathway, especially p38MAPK, and promotes the polarization of microglia to the M1 type, releasing a large amount of inflammatory factors such as TNF-α and IL-1β, thereby exacerbating neuroinflammation and pain.[49] In addition, the activation of p38MAPK also induces microglia to release BDNF. Besides weakening inhibitory signal transduction through the TrkB pathway, BDNF also promotes NP by synergistically inducing M1 polarization of microglia.[50] After activation of P2X7 receptor, potassium ion efflux is allowed, promoting NLRP3 inflammasome assembly and activation, cleaving precursor IL-1 β and precursor IL-18 into active forms and releasing them, which helps microglia polarize towards M1 type.[51] The use of P2X7R antagonists to inhibit P2X7 expression can alleviate NP and promote the polarization of microglia to M2 type and inhibit M1 type both in vivo and in vitro.[52]

Chemokine Signaling Pathway

The chemokine signaling pathway plays an important role in regulating the migration, activation, and polarization of microglia, and is closely related to NP. Microglia crosstalk with neurons and astrocytes through chemokine signaling pathways. After nerve injury, primary afferent fibers and local neurons in the spinal cord can release CX3CL1 and CCL2, which interact with microglial receptors CX3CR1 and CCR2, thereby initiating downstream signal transduction.[53] In addition, astrocytes can also release CCL2 to modulate microglial activity.[53] p38MAPK is a crucial downstream kinase of the CX3CL1/CX3CR1 and CCL2/CCR2 signaling axes. Once activated, it can prompt microglia to polarize towards the M1 type, secrete more pro-inflammatory factors, thereby exacerbating neuroinflammation and NP.[54] Blocking chemokine signaling pathways through intrathecal injection of CX3CR1 and CCR2 neutralizing antibodies can reduce abnormal migration and M1 polarization of microglia and alleviate NP symptoms.[53,55]

Notch Signaling Pathway

The Notch signaling pathway is composed of Notch receptors, Notch ligands and effector molecules. Research indicates that the Notch signaling pathway not only plays a crucial role in the regulation of neural development but also participates in the pathogenesis of NP by regulating microglial activation and polarization.[56] After nerve injury, Notch receptors bind to their ligands, and Notch receptors are cleaved by γ-secretase, releasing the Notch intracellular domain (NICD). NICD translocates into the nucleus, where it associates with recombination signal-binding protein Jκ (RBP-Jκ) to form a transcriptional activation complex. This complex promotes the expression of interferon regulatory factor 8 (IRF8), which facilitates the production of inflammatory mediators and drives the rapid polarization of microglia toward the M1 type.[56] In animal models of NP, inhibition of the Notch/RBP-Jκ signaling pathway reduced M1 polarization and inflammation of spinal microglia and improved pain symptoms.[27]

NLRP3 Inflammasome Signaling Pathway

The NLRP3 inflammasome is composed of NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), and the precursor of caspase-1. Under NP conditions, multiple stimulating factors can activate the NLRP3 inflammasome, such as ROS produced by mitochondrial dysfunction after nerve injury, intracellular potassium ion efflux, and ATP release. Activated NLRP3 recruits ASC and Caspase-1 precursor to form an active NLRP3 inflammasome complex, which can cleave Caspase-1 precursor to activate it.[57] Once activated, caspase-1 cleaves the immature precursors of IL-1β and IL-18, converting them into active IL-1β and IL-18 and releasing them, which induces microglia to polarize towards the M1 type, triggering intense neuroinflammation and thereby exacerbating NP symptoms. Inhibiting the activation of NLRP3 with NLRP3 inhibitors can reduce the release of IL-1β and IL-18, and suppress the M1 polarization of microglia, providing an important target for the treatment of NP.[58]

Signal Transducer and Activator of Transcription (STAT) 3 Signaling Pathway

The STAT family plays a crucial role in the signal transduction of cytokines and growth factors. Comprising seven members, the STAT family includes STAT3, a central mediator of microglial activation and neuroinflammatory responses.[59] In resting microglia, STAT3 remains in an inactive state. When stimulated by cytokines such as IL-6, microglial surface receptors undergo dimerization, leading to the activation of associated Janus kinase (JAK). JAK-mediated phosphorylation of specific tyrosine residues on STAT3 enables the formation of STAT3 homodimers or heterodimers, which subsequently translocate into the nucleus to regulate the transcription of inflammatory genes. Studies have shown that the increased release of inflammatory factors caused by the activation of the JAK2/STAT3 signaling pathway in microglia is closely related to the development of NP.[60] SOCS3 serves as a negative regulator of STAT3. Studies have demonstrated that increasing the expression of SOCS3 in the spinal cord can inhibit the phosphorylation of STAT3, suppress the M1 polarization of microglia, and promote the M2 polarization to alleviate NP.[61]

Peroxisome Proliferator-Activated Receptor γ (PPARγ) Signaling Pathway

PPARγ belongs to the nuclear receptor superfamily and is typically found in the cytoplasm in an inactive form. Upon ligand binding, PPARγ undergoes a conformational change, allowing it to translocate into the nucleus and form a heterodimer with the retinoid X receptor (RXR). This heterodimer then recognizes the peroxisome proliferator-activated receptor response elements in the promoter regions of target genes, thereby regulating gene transcription.[62] In microglia, activation of the PPARγ signaling pathway suppresses the activity of inflammation-related signaling pathways such as NF-κB and MAPK, decreases the expression of M1 polarization and pro-inflammatory cytokines such as TNF-α, IL-1β, and iNOS, and simultaneously promote the expression of M2 polarization markers such as IL-10, TGF-β, and Arg-1, thereby driving microglia towards anti-inflammatory M2 polarization.[63,64] In NP research, administration of PPARγ agonists can alleviate neuroinflammation and relieve pain.[65]

Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Signaling Pathway

The Nrf2 signaling pathway is an important intracellular antioxidant stress and anti-inflammatory regulatory pathway. Under normal conditions, Nrf2 binds to Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm, where it undergoes continuous ubiquitination and proteasomal degradation. Upon exposure to oxidative stress or inflammatory stimuli, microglia experience modifications in the cysteine residues of Keap1, leading to a conformational change that results in the release of Nrf2. The liberated Nrf2 translocates into the nucleus and binds to antioxidant response elements, initiating the transcription of a series of antioxidant and anti-inflammatory genes, such as heme oxygenase-1 (HO-1) and NADPH: quinone oxidoreductase 1 (NQO1). These gene products exert antioxidant and anti-inflammatory effects, inhibit the polarization of microglia to the M1 type, and promote their polarization to the M2 type.[66] In the NP model, activating the Nrf2 signaling pathway can alleviate neuroinflammation and relieve pain symptoms.[67] Therefore, enhancing Nrf2 activity may offer a promising strategy to restore the balance of microglial polarization during NP progression.

Colony-Stimulating Factor 1 Pathway

Following peripheral nerve injury, sensory neuron-derived colony-stimulating factor 1 (CSF1) activates both resident microglia in the spinal cord and resident macrophages in the dorsal root ganglion (DRG) by binding to the CSF1 receptor (CSF1R) expressed on the surface of these cells.[68] In animal studies, intrathecal administration of CSF1 directly induces mechanical hypersensitivity in mice,[69] while intracisternal injection of CSF1 antibody blocks long-term potentiation (LTP) in the spinal dorsal horn induced by high-frequency stimulation.[70] Studies have indicated that CSF1R inhibitors can suppress M1 microglial polarization while increasing the M2/M1 polarization ratio, thereby attenuating central inflammatory responses. These findings demonstrate the involvement of CSF1/CSF1R signaling in regulating microglial polarization, suggesting its potential as a key mechanism governing microglial polarization in NP.[71,72]

NP Therapeutic Strategies for Regulating Microglial Polarization

Drug Intervention

Pharmacological treatment remains the most commonly utilized therapeutic strategy for NP. A wide range of pharmacological agents can modulate the phenotype transformation of microglia by regulating the aforementioned signaling pathways. In recent years, especially, traditional Chinese medicine (TCM) components have demonstrated significant regulatory capabilities in the polarization of microglia. Both single TCM compounds and complex TCM formulations have demonstrated anti-inflammatory and analgesic effects across various NP models such as SNI, CCI, DPN, and CIPN by regulating the M1/M2 polarization of microglia in the spinal cord and brain. Furthermore, certain synthetic drugs have also been shown to influence microglial polarization, albeit to a lesser extent.

Natural Medicines (Single Components and Formulations of Traditional Chinese Medicine)

In the SNI rat model, sodium tanshinone IIA sulfonate (STS) significantly increased mechanical pain threshold, upregulated miR-125b-5p and Arg-1 expression in the spinal dorsal horn, inhibited STAT3 phosphorylation, and reduced levels of pro-inflammatory cytokines and CD68; In vitro experiments have confirmed that STS inhibits LPS induced inflammation in BV-2 cells and promotes M2 polarization by enhancing miR-125b-5p, indicating that STS exerts anti-

inflammatory and analgesic effects by regulating microglial phenotype transformation.[59] miR-125b-5p was specifically expressed in microglia and promoted microglia activation by inhibiting the target gene A20.[73] STS regulates miR-125b-5p to specifically mediate microglial polarization. The NF-κB and MAPK pathways are key pathways that regulate polarization of microglia, and are regulated by various TCM in different NP models. Oleanolic acid blocks spinal cord TLR4/NF-κB signaling, reduces the release of pro-inflammatory factors and promotes microglial transformation to M2 type, thereby improving hyperalgesia in SNL mice.[74] Paeonol alleviates neuropathic pain in CCI rats by regulating M1/M2 polarization of spinal microglia through the RhoA/p38MAPK signaling pathway.[75] In addition, morin inhibits neuroinflammation by regulating the polarization of M1/M2 microglia in the cerebral cortex through the suppression of the NF-κB signaling pathway, thereby alleviating vincristine-induced neuropathic pain.[76] Daphnetin can inhibit LPS induced M1 polarization increase and M2 polarization decrease in human HMC3 microglia in vitro, and alleviate TNF-α - induced rat NP by suppressing the CX3CL1/CX3CR1 pathway to inhibit M1 polarization and promote M2 polarization in spinal microglia in vivo.[77] Dehydrocorybulbine also alleviates bone cancer pain in mice by promoting M1 polarization and inhibiting M2 polarization of spinal microglia.[78] In addition, various TCM monomers, such as dihydromyricetin,[79] curcumin,[80] and the traditional Chinese medicine formulas such as Huangqin Decoction[81] and Duhuo Jisheng Decoction[82] also exhibit the above mechanism. They agents alleviate NP by modulating multiple signaling pathways and inhibiting the M1/M2 polarization balance of microglia.[80] Additionally, traditional Chinese medicine formulations such as Huangqi Guizhi Wuwu Decoction for diabetes-induced neuropathic pain and Buyang Huanwu Decoction for herpes zoster-related neuropathic pain have also demonstrated therapeutic potential.[83]

Synthetic Drugs

Minocycline can alleviate facial pain sensitivity and cognitive deficits in rats with trigeminal neuralgia, and its mechanism of action is associated with the regulation of microglial polarization. In both in vivo and in vitro experiments, minocycline polarizes activated microglia to the M2 phenotype through the TLR4/MyD88/NF-κB pathway, reducing pro-inflammatory factors IL-1β and IL-6 and increasing anti-inflammatory factors IL-4 and IL-10, thereby alleviating neuroinflammation.[84] Another study demonstrated that minocycline improved pain-related emotional disorders induced by CCI in mice by continuously down-regulating FosB expression in the ventral hippocampus and inhibiting M1 polarization of microglia in the medial prefrontal cortex.[85] In the CCI model, lidocaine has been observed to ameliorate neuropathic pain by suppressing M1 microglial polarization to reduce pro-inflammatory cytokine expression and concurrently promoting M2 polarization to modulate the inflammatory microenvironment.[86] In the SNI mouse model, melatonin (MLT) administered via intraperitoneal injection or direct injection into the anterior cingulate cortex (ACC) dose-dependently alleviated neuropathic pain symptoms. Mechanistically, MLT activates the Gα(i) signaling pathway to inhibit the excitability of ACC pyramidal neurons, while suppressing the M1 pro-inflammatory phenotype and promoting the M2 anti-inflammatory phenotype to reduce ACC inflammation and type II interferon responses, revealing a novel mechanism of MLT's neuro-immune regulation.[87] Researchers have reported that cerium oxide nanoparticles alleviate neuropathic pain by promoting M2 microglial polarization while suppressing M1 phenotype expression, offering novel insights into NP treatment strategies.[88] Clinically, anticonvulsants such as gabapentin are commonly used to manage neuropathic pain. When side effects are not a primary concern, tricyclic antidepressants (eg, amitriptyline) or even opioid analgesics (particularly in palliative care settings) may be administered.[89]

Neural Regulation

Electroacupuncture(EA), as an effective therapeutic approach for NP, has been widely used in clinical practice, but its mechanism of action remains incompletely understood. In SNL rats, EA significantly increased mechanical/thermal pain thresholds, reduced myelin structure damage, upregulated PD-L1 expression in the spinal cord, inhibited MAPK pathway activation, and promoted the transformation of microglia from pro-inflammatory M1 to anti-inflammatory M2 phenotype; knockdown of PD-L1 reversed the analgesic effect of EA.[90] In SCI rats, transcranial direct current stimulation (tDCS) improve motor function and hyperalgesia, reduce the levels of pro-inflammatory factors in brain regions such as the cortex and thalamus, increase the expression of anti-inflammatory factors in the thalamus, and promote the

transformation of microglia in regions such as the ventral posterolateral nucleus (VPL) from pro-inflammatory M1 to anti-inflammatory M2 type.[30]

Discussion

Microglial polarization plays a pivotal role in the initiation and progression of NP. M1-type microglia mediate neuroinflammation and hyperalgesia by secreting pro-inflammatory factors, while M2-type microglia suppress inflammatory responses, promote neural repair and relieve pain by secreting anti-inflammatory factors. Despite significant advances in understanding the relationship between microglial polarization and NP, several gaps and challenges remain in this field. Firstly, the precise regulatory mechanism underlying microglial polarization remain incompletely understood. Although multiple signaling pathways and various regulatory factors have been identified to participate in this process, the intricate interaction network among these components has yet to be thoroughly elucidated. Furthermore, the involvement of microglia in the pathogenesis of neuropathic pain (NP) demonstrates sexual dimorphism. For instance, intrathecal administration of P2X4 receptor antagonists has been shown to attenuate CCI-induced pain hypersensitivity exclusively in male rats.[91] In contrast to male rats, the mRNA and protein level of P2X4 in spinal microglia of female rats do not upregulated after neuropathy, and pain development occurs through a lymphocyte-dependent mechanism rather than via microglial P2X4 activation.[92] The underlying basis for this sex-based difference may involve hormonal and genetic factors. Whether gender differences exist in the therapeutic effects of interventions targeting microglial polarization in NP remains to be further elucidated. Secondly, current intervention strategies require further validation regarding their safety and effectiveness. Whether through pharmacological treatment or other modalities, clinical applications may encounter challenges such as adverse effects and variability in individual responses. Notably, a clinical trial investigating the microglial inhibitor minocycline in chronic low back pain patients found that 14-day administration neither induced changes in cerebral translocator protein signals measured by positron emission tomography (PET) imaging nor reduced self-reported average daily pain. The therapeutic efficacy of glial modulators for human pain control remains inadequately established and underexplored, highlighting a critical knowledge gap that warrants collaborative investigation between basic and clinical research.[93]

Age-dependent microglial polarization represents a critical factor modulating neuropathic pain. Two-photon in vivo imaging reveals a 40% reduction in microglial process motility within the cortex of aged mice, coupled with accelerated and less reversible M1 polarization following injury. These alterations are directly associated with downregulation of the CX3CL1-CX3CR1 signaling axis.[94] Genetic background significantly influences microglial polarization dynamics. Xuan et al systematically compared three mouse strains (C57BL/6, BALB/c, and 129/Sv) and found that BALB/c exhibited the lowest baseline P2X4 receptor expression in microglia. Following nerve ligation, this strain showed the weakest upregulation of the M2 marker Arg1, resulting in prolonged mechanical hypersensitivity lasting >8 weeks.[95] These findings underscore how strain selection can directly impact experimental outcomes in neuropathic pain research. In the future, research on microglial polarization and NP is anticipated to make breakthroughs in the following directions. First, further investigation into the molecular mechanisms underlying microglial polarization is needed to identify more precise therapeutic targets, facilitate the development of novel drugs that specifically modulate key signaling pathways or molecules, and enable precise regulation of microglial polarization. Second, the integration of multi-omics approaches, including transcriptomics, proteomics, and single-cell omics, will allow for a comprehensive characterization of the spatiotemporal dynamics of microglial polarization under NP conditions, thereby providing a scientific basis for the development of personalized treatment strategies. Third, increased efforts should be directed toward exploring emerging technologies and therapeutic modalities, such as nanomedicine delivery systems and immunomodulatory therapies, with the aim of optimizing treatment protocols, enhancing therapeutic efficacy, minimizing adverse effects, and accelerating their translation from bench to bedside.

Conclusion

Microglial polarization plays a central regulatory role in NP, where M1 phenotype promotes pain and M2 phenotype exerts analgesic effects, with their balance finely regulated by complex signaling networks. Current interventions targeting polarization—through pharmacological, neuromodulatory, and physical approaches—have emerged as

promising strategies for NP management. However, challenges remain, including the complexity of polarization networks, spatiotemporal dynamics, region-specificity, and sexual dimorphism. Future studies should integrate multi-omics and targeted delivery technologies to decipher microglial heterogeneity and advance precision therapies for NP. Targeting microglial polarization not only deepens our understanding of NP mechanisms but also opens new avenues for innovative analgesic treatments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interest.

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