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Neuropathic pain through the perspective of microglia–neuron interactions: a translational review for clinicians

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ABSTRACT

Background/importance Neuropathic pain affects up to 10% of the population and is often refractory to current treatments. Growing evidence implicates neuroimmune interactions, particularly microglia, in the pathophysiology, but their role is underappreciated in clinical practice.

Objective To summarize current evidence for microglial contributions to neuropathic pain, emphasizing microglia–neuron interactions and translational implications for clinicians.

Evidence review This narrative review synthesizes preclinical and emerging human data (postmortem histopathology, glial-signal positron emission tomography (PET) imaging, dorsal root ganglion transcriptomics) to examine microglial contributions to pain initiation, maintenance and resolution, sex differences and therapeutic implications.

Findings Preclinical evidence demonstrates that microglia are necessary and sufficient for pain initiation. Nerve injury engages central sensitization through colony-stimulating factor 1 (CSF1)–CSF1 receptor (CSF1R), purinergic receptors, damage-associated molecular pattern/Toll-like receptor signaling, cytokine cascades (TNFα, IL-1β, IL-6), prostaglandin E_2, extracellular matrix and synaptic remodeling and brain-derived neurotrophic factor–tropomyosin receptor kinase B-mediated disinhibition. Microglia also contribute to pain resolution via pro-resolving mediators and stimulator of interferon genes (STING)/interferon signaling. Sex differences are prominent: microglial mechanisms predominate in males, whereas T-cell-mediated pathways prevail in females. Human postmortem and glial-signal imaging studies support glial involvement in chronic pain but lack direct validation of specific microglial targets.

Conclusions Microglia coordinate pain initiation and resolution via conserved, drug-addressable pathways. Three translational implications emerge: (1) neuroimmune interventions are most effective early, given that microglia drive initiation more than maintenance; (2) sex-stratified trial designs are warranted given divergent microglial versus T-cell mechanisms by sex and (3) CSF1R-PET imaging may enable mechanism-based patient selection. These implications require prospective clinical validation.

INTRODUCTION

Chronic pain is a major global health problem that impairs quality of life and carries a substantial economic burden.[1 2] Neuropathic pain alone affects up to 10% of the population.[2 3] Current pharmacologic and interventional options often provide incomplete and unpredictable relief.

Conventional 'neuro-centric' frameworks emphasize abnormal firing of injured nerves and plasticity of nociceptive circuits. Over the past two decades, evidence has established the neuroimmune interface, defined as bidirectional crosstalk between immune/immunocompetent cells and nociceptive circuits, as a central driver of both pain initiation and persistence.[4–6] Microglia, the resident immune cells of the central nervous system (CNS), are especially important in this respect. They release proinflammatory and proresolution mediators, reshape the extracellular matrix and synapses to change synaptic transmission and neuronal excitability in the dorsal horn.[7–10]

Despite growing preclinical and emerging human data implicating neuroimmune mechanisms in neuropathic pain, microglia rarely enter clinical reasoning because we lack routine biomarkers and microglia-specific therapies.[11–13]

While several recent reviews have broadly surveyed the basic science of microglia in neuropathic pain, these are written primarily for a research audience.[8 9 14] The present review is unique in three respects: (1) it is written explicitly for clinicians unfamiliar with neuroimmune biology; (2) it uses preclinical evidence to reinterpret existing clinical treatments—steroids, biologics, neuromodulation—through a microglial lens, rather than cataloging only future drug targets and (3) it synthesizes clinically actionable concepts including disease-stage timing, sex-informed stratification and the distinction between microglial depletion and reprogramming, which have direct bearing on trial design and patient selection. In this narrative review, we examine microglia-nociceptor crosstalk, mechanisms linking peripheral nerve injury to central sensitization, microglial programs involved in pain resolution and emerging evidence for sex differences, with key pathways and candidate clinical agents summarized in table 1 (figures 1 and 2).

MICROGLIA SURVEILLANCE AND THE TIMING OF NEUROPATHIC PAIN

Sentinels that remodel neural circuits

Microglia arise from yolk-sac progenitors. They seed the CNS early in development and self-renew locally throughout life.[15] In the healthy adult, microglia continuously extend and retract their processes, 'sampling' the microenvironment.[16] This

Table 1 Major Microglia–neuron signaling pathways in neuropathic pain: preclinical evidence, clinical agents and translational status

Pathway/mechanism	Key preclinical evidence	Clinical drug or agent	Translational status/clinical caveat
CSF1–CSF1R signaling	CSF1 from injured DRG neurons drives microglial proliferation and activation; CSF1R blockade attenuates allodynia in rodent models[18 20]	CSF1R inhibitors (eg, pexidartinib, approved for tenosynovial giant-cell tumor)	No pain trials; hepatotoxicity risk; CNS penetrance variable
DAMPs/toll-like receptors (TLR2, TLR4)	Nerve-injury-released DAMPs (HMGB1, HSP60) activate microglial TLR2/4; NF-κB-driven cytokine release and central sensitization[28–30]	TLR4 antagonists (preclinical); no approved TLR-targeting analgesics	TLR4 on peripheral macrophages; systemic blockade risks immunosuppression; CNS-restricted delivery needed
ATP/purinergic receptors (P2X4, P2X7, P2Y12)	P2X4/P2X7 activation drives microglial BDNF release and p38 MAPK; P2Y12 guides process extension[21 31–33]	P2X7 antagonists in early trials; P2Y12 antagonists (clopidogrel, approved for thrombosis)	Receptors broadly expressed; P2Y12 antagonists (eg, clopidogrel) carry significant antiplatelet and bleeding risk, limiting their repurposing for CNS indications; P2X7 antagonists lack this liability. Sex specificity (male-predominant) warrants stratified trial design.
Pro-inflammatory cytokines (TNFα, IL-1β, IL-6)	Intrathecal cytokines sufficient to produce pain; blockade attenuates hypersensitivity in neuropathic models[10 38]	Anti-TNF biologics; IL-6R antagonists (tocilizumab); IL-1 receptor antagonists (anakinra)	Small trials show modest benefit for radiculopathy; systemic immunosuppression; low CNS bioavailability of large molecules
Prostaglandin E_2 (COX-2/EP receptors)	Microglial COX-2-derived PGE_2 potentiates NMDA currents in dorsal horn; EP2/EP4 blockade reduces sensitization[39]	NSAIDs; COX-2 inhibitors (celecoxib); EP4 antagonists in development	Widely used but not microglia-specific; long-term use limited by GI/cardiovascular risk
BDNF–TrkB–KCC2 axis	Microglial BDNF activates TrkB, downregulates KCC2, converting GABAergic input from inhibitory to excitatory[44 45]	TrkB antagonists (preclinical); KCC2 enhancers (preclinical)	Male-predominant preclinical evidence; BDNF–TrkB–KCC2 axis not validated in human spinal cord; TrkB antagonists and KCC2 enhancers remain preclinical.
Specialized pro-resolving mediators (resolvins)	Omega-3-derived resolvins reduce nociceptor excitability and microglial neuroinflammation; reverse allodynia in CIPN and CRPS models[50–52]	Omega-3 supplementation; resolvin analogs (preclinical)	No large RCTs for neuropathic pain; omega-3 safe but effect size uncertain
STING/type-I interferon pathway	Microglial STING activation after nerve injury releases type-I interferons; STING KO delays resolution; effects more prominent in males[53–55]	STING agonists in oncology trials; no pain-specific agents yet	Pain-resolving role context-dependent; systemic activation risks cytokine storm; sex-specific efficacy anticipated
Complement/C1q synaptic pruning	Microglia-mediated complement-dependent synaptic pruning in dorsal horn may contribute to neuropathic circuit remodeling[43]	Complement inhibitors (eg, eculizumab); investigational C1q-blocking antibodies	Highly speculative for pain; complement pathway broadly expressed; CNS penetrance of current inhibitors limited

ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; BDNF, brain-derived neurotrophic factor; CIPN, chemotherapy-induced peripheral neuropathy; CNS, central nervous system; COX-2, cyclooxygenase-2; CRPS, complex regional pain syndrome; CSF1, colony-stimulating factor 1; CSF1R, CSF1 receptor; DAMP, damage-associated molecular pattern; DRG, dorsal root ganglion; EP, Eicosapentaenoic; IL-6, interleukin-6; IL-1β, interleukin-1β; KCC2, potassium-chloride cotransporter 2; KO, knock out; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-B; NMDA, N-methyl-D-aspartate; NSAIDs, non-steroidal anti-inflammatory drugs; PGE, prostaglandin; RCTs, randomized control trials; STING, stimulator of interferon genes; TNFα, tumor necrosis factor alpha.

surveillance is not just passive housekeeping; microglia actively prune, strengthen and help maintain synaptic connections.[7]

Microglia are now recognized as central mediators of neuroinflammation across CNS disease states, including chronic pain.[4] Early work showed that glial-derived cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) are sufficient to induce pain behaviors when applied intrathecally, linking microglial activation to central sensitization long before we could visualize these neuroimmune interactions in vivo.[10]

Microgliosis versus microglial activation

Peripheral nerve injury in rodents reliably produces pain behaviors reminiscent of human traumatic neuropathy or complex regional pain syndrome (CRPS) type 2. These injuries trigger microgliosis in the ipsilateral dorsal horn, characterized by an increase in microglial number and a shift from ramified to amoeboid morphology.[17] Microgliosis is a useful histologic marker, but it does not necessarily equate to functional activation. In rodent neuropathy models, pain hypersensitivity develops within 1 day of nerve injury, whereas microgliosis is not appreciable until day 2 and peaks between 7 and 14 days postinjury—this timing dissociation indicates that early microglial activation, rather than proliferation per se, is the functionally critical event.[7 8 17]

More refined experiments have distinguished proliferation and morphologic changes from functional activation. Genetic or pharmacologic manipulation of the transcription factor c-Myc reduces early microglial proliferation and attenuates mechanical hypersensitivity, suggesting that proliferation is not merely an epiphenomenon of nerve injury. Yet some manipulations that blunt microgliosis leave pain intact, indicating that what microglia do may be more important than simply the absolute number.[17–19]

In preclinical models, converging evidence indicates that microglial activation is both necessary and sufficient for pain initiation. Necessity is demonstrated by the finding that interfering with microglial activation through deletion of the adaptor protein DAP12 prevented mechanical hypersensitization after nerve injury without equivalently reducing microglial number.[18 20] Sufficiency is demonstrated by the finding that intrathecal transfer of activated microglia, or chemogenetic or optogenetic activation of spinal microglia, can evoke allodynia in otherwise uninjured animals.[21–23] In rodent models, selective depletion of microglia around the time of nerve injury also reduces mechanical hypersensitivity; as microglia repopulate the spinal cord, pain behaviors re-emerge.[20]

Inhibition of microglia with the antibiotic minocycline attenuates mechanical hypersensitivity after nerve injury in rodents. However, clinical trials of minocycline for neuropathic pain have shown limited benefit, likely because it is not microglia-specific, has significant off-target effects and is initiated well after the early microglia-driven phase of injury.[24 25] This disconnect

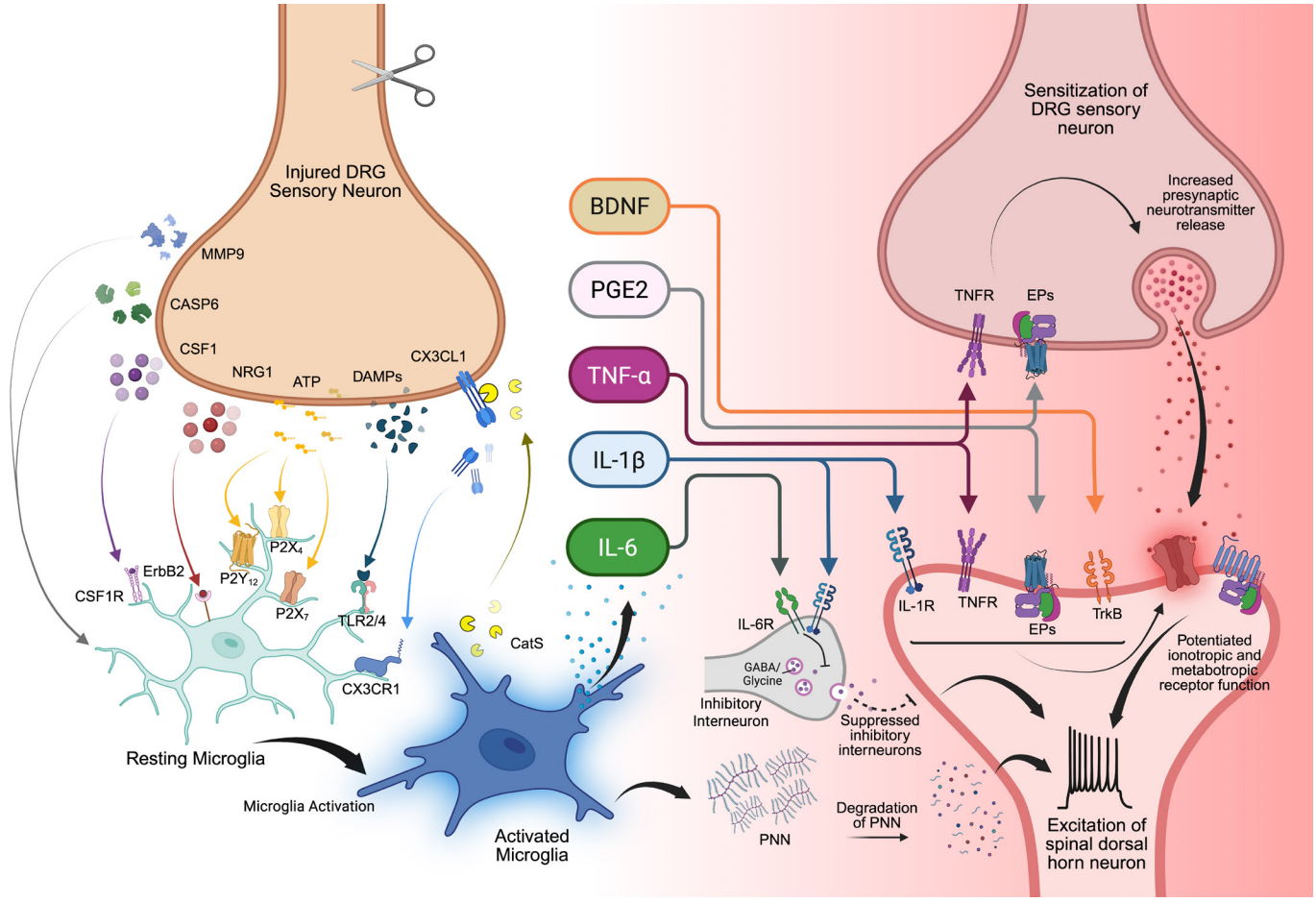

Figure 1 Microglia–neuron interactions in the spinal dorsal horn. Following peripheral nerve injury, primary sensory neurons release mediators from their presynaptic terminals in the dorsal horn that engage receptors on resting microglia, leading to microglial activation. Colony-stimulating factor 1 (CSF1) binds to CSF1R, CX3C-chemokine ligand 1 (CX3CL1) to CX3CR1 and damage-associated molecular patterns (DAMPs)—including heat-shock proteins (HSPs), fibronectin, and high-mobility group box 1 (HMGB1)—to toll-like receptors 2 and 4 (TLR2/4). Adenosine triphosphate (ATP), acting as both a neurotransmitter and a DAMP, activates microglia via purinergic receptors P2X4 and P2X7. Additional activators include neuronally released matrix metalloproteinase-9 (MMP9) and caspase-6 (CASP6). Neuregulin 1 (Nrg1) activates Erb-b2 receptor tyrosine kinase 2 (ErbB2). Activated microglia release proinflammatory mediators that enhance the excitability of second-order dorsal horn neurons by modulating synaptic receptors, suppressing inhibitory interneurons, and increasing presynaptic neurotransmitter release. Interleukin-1β (IL-1β) acts via IL-1R, interleukin-6 (IL-6) via IL-6R, prostaglandin E_2 (PGE_2) via EP receptors, and tumor necrosis factor-α (TNFα) via TNFR. Cathepsin S (CatS) released from microglia cleaves CX3CL1 in a feed-forward loop. Brain-derived neurotrophic factor (BDNF) binds TrkB receptors, causing a depolarizing shift in the anion reversal potential and contributing to disinhibition. Activated microglia also degrade perineuronal nets (PNNs), further promoting hyperexcitability. Created in BioRender. Su, P. (2026) https://BioRender.com/j15s544

between strong preclinical and modest clinical effects illustrates how timing and specificity matter.

These translational gaps reflect broader challenges inherent in preclinical pain models: species-specific features of microglial activation, the absence of patient-level factors such as age, sex, analgesic exposure and comorbidities that substantially shape neuroimmune responses. These differences do not invalidate the preclinical findings discussed here, but they argue for caution in assuming that preclinical efficacy predicts clinical benefit.

In rodent models, microglia appear to play a more limited role in the maintenance of chronic pain. Inhibition or depletion is most effective when applied early; later intervention often fails to reverse established hypersensitivity or produces only transient relief.[26] Peripheral monocytes and other CNS cells may take over in later stages of pain, and specific microglial subsets contribute toward pain recovery.[27]

Clinical relevance—timing matters

If microglia are most important for the initiation rather than the maintenance of neuropathic pain, microglia-targeted interventions are most likely to help when deployed in an early window after injury (eg, around surgery, acute trauma or new-onset radicular pain) rather than years into established chronic pain.[4 8]

PATHWAYS THAT COUPLE NOCICEPTORS TO MICROGLIA

At a molecular level, injured nerves and active dorsal horn circuits engage microglia via signaling pathways conserved across multiple immune cell types. Thus, drugs developed for autoimmune diseases and cancers already target several nodes in these pathways, making them strong candidates for repurposing for pain treatment (table 1).

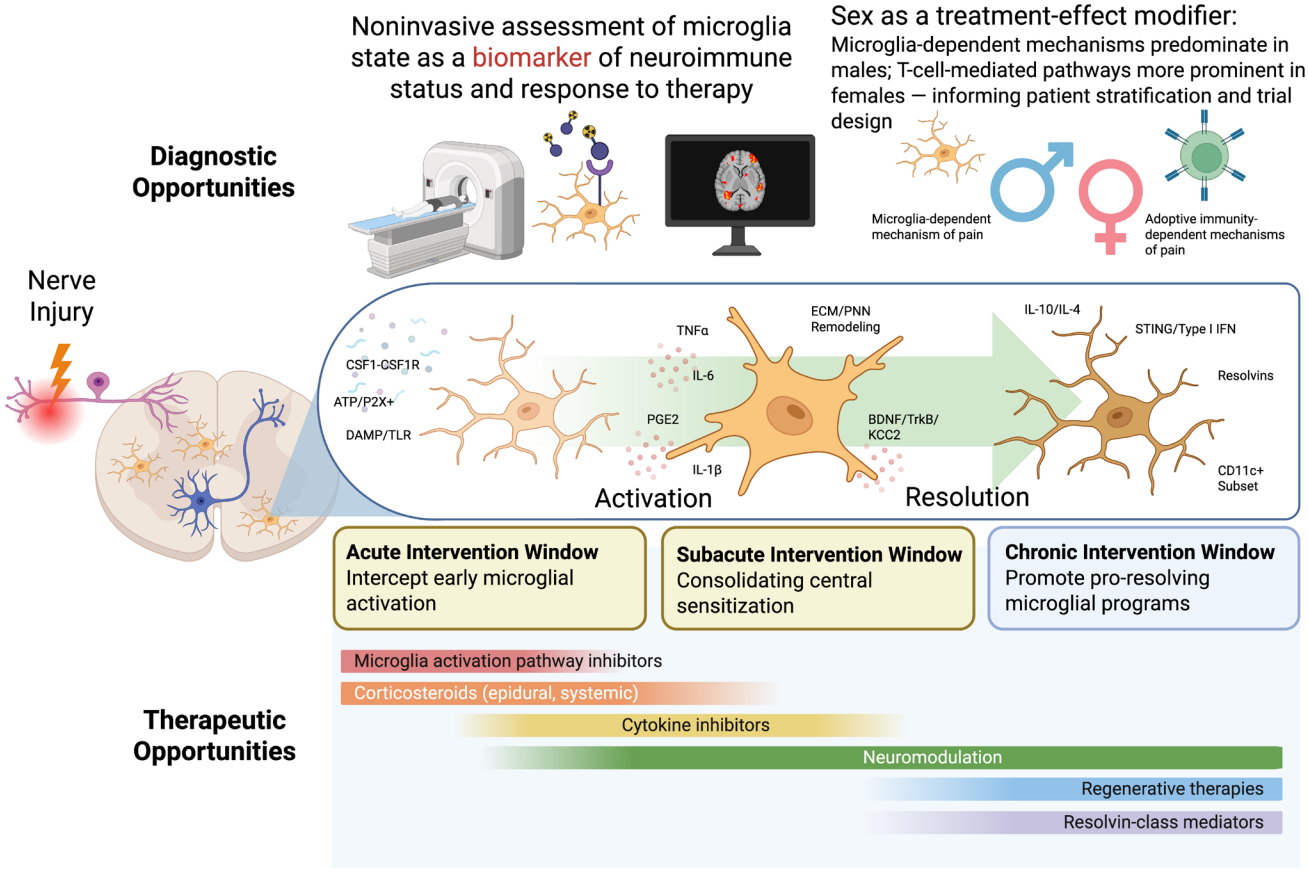

Figure 2 A Conceptual three-stage framework for neuroimmune-informed neuropathic pain management. This figure is intended as a heuristic for clinical reasoning and trial design; it does not constitute a clinical practice guideline. Diagnostic opportunities (top row). Emerging approaches for noninvasive neuroimmune profiling include molecular imaging (eg, TSPO-PET for microglial activation), functional neuroimaging and circulating biomarkers, which can be used to guide patient selection and to assess therapy response. Sex is depicted as a cross-cutting biological modifier, reflecting preclinical evidence that microglial mechanisms predominate in males while adaptive immune pathways predominate in females. Therapeutic opportunities (bottom row). Stage 1: acute/perioperative (0–2 weeks). Microglia appear to be most critical during the initiation phase of neuropathic pain. High-risk patients (postsurgical, traumatic nerve injury, acute radiculopathy) may benefit most from early neuroimmune-modulating interventions timed to this window. Anti-inflammatory agents and activation pathway inhibitors specifically target the essential role of microglia during this stage (eg, CSF1-CSF1R, DAMP-TLR, purinergic signaling, corticosteroids). Stage 2: subacute (2–12 weeks). Microgliosis peaks (days 7–14 in rodent models) and central sensitization consolidates. Cytokine-targeted biologics (eg, anti-TNFα/IL-1/IL-6) may be most relevant in this window to interrupt the pronociceptive signals from activated microglia. Stage 3: Chronic (>12 weeks). Although microglia appear less essential for the maintenance of established chronic pain, later-stage therapeutic goal shifts to promoting pro-resolving microglial programs. Strategies include resolvin-class mediators (eg, omega-3 fatty acid-derived resolvins), regenerative approaches (eg, platelet-rich plasma (PRP) and mesenchymal stem cells (MSC)) and neuromodulation to activate resolution pathways (eg, IL-4/10 signaling, STING/type I interferon), and expansion or reprogramming of pain-resolving microglia subsets (eg, CD11c+). ATP adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CSF1, colony-stimulating factor 1; CSF1R, CSF1 receptor; DAMP, damage-associated molecular pattern; ECM, extracellular matrix; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; KCC2, potassium-chloride cotransporter 2; PGE_2, prostaglandin E_2; PET, positron emission tomography; PNN, perineuronal net; STING, stimulator of interferon genes; TNFα, tumor necrosis factor alpha; TLR, toll-like receptor; TSPO, translocator protein (18 kDa kDa). Created in BioRender. Su, P. (2026) https://BioRender.com/i9li1ww

CSF1-CSF1R signaling

After peripheral nerve injury, sensory neurons upregulate colony-stimulating factor 1 (CSF1) and deliver it to dorsal horn terminals, where CSF1 receptor (CSF1R) signaling drives microglial activation and proliferation. Deletion of neuronal CSF1 or CSF1R blockade prevents microglial activation and pain behaviors, confirming CSF1R as a major upstream driver of the pain-initiating microglial state described above.[18 20]

DAMPs and toll-like receptors

Nerve injury releases damage-associated molecular patterns (DAMPs), including heat shock proteins, fibronectin and high-mobility group box 1 (HMGB1), that activate toll-like receptors (TLRs), particularly TLR2 and TLR4, expressed by microglia and other CNS cells. Genetic deletion or pharmacologic inhibition of TLR2 or TLR4 reduces microglial activation and attenuates mechanical allodynia in several

neuropathic models.[28–30] However, because TLRs are also expressed on astrocytes, neurons and other immune cells, the specificity of microglial-mediated DAMP signaling in pain behavior remains uncertain.

ATP and purinergic receptors

ATP is released by neurons and glia after injury and during intense synaptic activity.[31 32] Microglia express several ATP-gated P2X and P2Y receptors. Among them, P2X4 and P2X7 are particularly important for neuropathic pain. Blocking these receptors reduces allodynia, whereas activation promotes proinflammatory mediator release.[21 33]

P2X7 activation in microglia triggers the release of the lysosomal protease cathepsin S (CatS), which cleaves the neuronal chemokine CX3C-chemokine ligand 1 (CX3CL1) into a soluble form.[34–36] Soluble CX3CL1 then binds to CX3CR1 on microglia, further amplifying neuroinflammation. Intrathecal CX3CL1 is sufficient to induce allodynia, and inhibition of CatS or CX3CR1 markedly reduces pain behaviors.[35 37]

Proinflammatory cytokines

Activated microglia release multiple proinflammatory cytokines (TNFα, IL-1β and IL-6) that drive sensitization of spinal dorsal horn circuitry: TNFα acts via TNFR1 and TNFR2 to increase glutamate release and potentiate both ionotropic and metabotropic glutamate receptors on second-order neurons to enhance excitatory postsynaptic currents.[10 38] IL-1β binds IL-1 receptors on second-order neurons to potentiate NMDA receptor function and suppresses inhibitory interneuron activity.[10 38] IL-6 acts through both membrane-bound and soluble IL-6 receptors (IL-6R) to suppress GABAergic and glycinergic transmission, reducing inhibitory postsynaptic currents and further tipping the balance towards excitation.[10]

Blocking any one of these cytokines can reduce neuropathic pain in animal models while administering them intrathecally can elicit allodynia in otherwise uninjured animals.[10 38] Cytokines also act in an autocrine manner on microglia, reinforcing their activation.[7 8]

Prostaglandin E_2

Prostaglandin E_2 (PGE_2), generated predominantly by cyclooxygenase-2 (COX-2), is another important mediator linking microglial activation to pain. PGE_2 acts on EP receptors to increase presynaptic neurotransmitter release and depolarize dorsal horn neurons.[39] These mechanisms contribute to the analgesic effects of COX-2 inhibitors and may partially underlie the benefits of local or neuraxial steroid injections that suppress COX-2 and downstream prostaglandins.

Extracellular matrix and synaptic pruning

The extracellular matrix (ECM) of the spinal cord includes perineuronal nets (PNNs) that surround and stabilize neurons. After nerve injury, neurons upregulate proteases such as matrix metalloproteinase-9 and caspase-6, and microglia themselves engage in ECM remodeling.[40 41] Recent work shows that microglia-mediated degradation of PNNs around projection neurons in the superficial dorsal horn is both necessary and sufficient for the development of pain behaviors.[42] Depleting microglia before nerve injury preserves PNNs and prevents mechanical and thermal hypersensitivity, whereas selectively digesting PNNs in the absence of nerve injury is enough to produce spontaneous pain and hyperalgesia. Functionally, PNN loss increases projection neuron excitability. A complementary structural mechanism involves microglial complement-mediated pruning of inhibitory synapses: C1q-dependent elimination of inhibitory synapses in the dorsal horn reduces inhibitory tone and contributes to pain behavior in preclinical models, with C1q inhibition attenuating this effect.[43] Together, PNN degradation and inhibitory synapse pruning indicate that microglia remodel pain circuits not only through soluble mediators but also by physically dismantling the structural elements that normally constrain nociceptive signaling.

BDNF and neuronal disinhibition

Brain-derived neurotrophic factor (BDNF) binds tropomyosin receptor kinase B (TrkB) receptors on pain projection neurons in the dorsal horn and downregulates potassium–chloride cotransporter 2 (KCC2), shifting the chloride reversal potential, so that GABAergic and glycinergic inputs, normally inhibitory, become depolarizing.[44 45] This disinhibition is a hallmark of central sensitization in neuropathic pain. However, the role of microglia as the source of BDNF remains genuinely contested: conditional deletion of BDNF specifically from microglia in some mouse lines does not eliminate neuropathic pain, suggesting that neurons or other glial cells may serve as alternative sources under certain experimental conditions.[44] The mechanism also appears sex-specific, with the BDNF–TrkB–KCC2 axis most consistently demonstrated in male rodents and weaker or absent effects in females.[44] Finally, although the pathway is well established in rodents, direct human validation is lacking: KCC2 downregulation and its functional consequences have not been demonstrated in the spinal cords of patients with neuropathic pain, and whether a microglia-dependent mechanism underlies any such change in humans remains unknown.

Clinical relevance—drug-addressable pathways

Many drugs developed for oncologic and autoimmune purposes target the aforementioned pathways.[5 7 8] Understanding when and how these pathways are engaged after nerve injury creates opportunities to repurpose existing agents or design new ones for microglia-focused pain therapy.

MICROGLIAL PROGRAMS FOR PAIN RESOLUTION

Anti-inflammatory and neonatal programs

In rodent models, neuropathic pain behavior is constitutively suppressed during early postnatal development, a period during which neonatal microglia maintain elevated anti-inflammatory cytokine production.[46] Neonatal microglia produce higher baseline levels of IL-4 and IL-10; experimental depletion of these signals unmasks adult-like pain responses to nerve injury, suggesting that microglia contribute to a developmental 'protective window'. Whether this finding has clinical relevance in understanding differential vulnerability to persistent pain in pediatric versus adult patients remains unknown.

Microglia can also contribute to pain resolution in adulthood. In a mouse model of CRPS, depletion of established adult microglia did not alter pain, but allowing microglia to repopulate the spinal cord led to full recovery.[47] Newly repopulated microglia exhibited a transcriptomic profile distinct from the original resident population, including differences in genes associated with inflammatory activation, suggesting that resetting microglial identity may be therapeutically beneficial.[47]

A specific microglial subset expressing the CD11c marker has been linked to pain remission.[48] These $CD11c^+$ microglia emerge approximately 2–4 weeks postinjury, coinciding temporally with the period of natural recovery and carry a transcriptomic profile enriched for homeostatic and anti-inflammatory genes,

distinct from the early proinflammatory population that drives pain initiation.[47] Depletion of CD11c$^+$ microglia in animals that had otherwise recovered triggers relapse of pain behavior, establishing that their role is active rather than merely a correlate of recovery.[48] IL-4 resurfaces in this context as necessary to expand this pro-resolving CD11c+ subset, identifying a tractable mechanism for IL-4-mediated analgesia in preclinical models.[49]

Specialized pro-resolving mediators and STING signaling

Microglia synthesize and release specialized pro-resolving mediators such as omega-3 fatty acid-derived resolvins. Resolvins can reduce nociceptor excitability and dampen inflammatory signaling, including via effects on microglia.[50 51] Resolvins reverse neuropathic pain in models of chemotherapy-induced peripheral neuropathy, CRPS and spinal cord injury.[50–52]

Microglia also engage the stimulator of interferon genes (STING) pathway, which serves as an example of how the same molecular target can drive opposing outcomes depending on timing. Early after nerve injury, microglial STING activation via proinflammatory NF-κB signaling promotes IL-6 release and contributes to pain initiation, whereas later STING activation engages type-I interferon signaling that decreases nociceptor excitability and promotes resolution.[53 54] This bidirectionality—the same pathway driving opposing outcomes depending on timing—makes STING particularly illustrative of why early versus late intervention may yield fundamentally different results, consistent with the broader pattern that microglial function depends on context and timing. STING-mediated resolution effects appear sex specific, with greater prominence in males.[54 55]

Clinical relevance—don't just 'turn microglia off.'

Because microglia also participate in resolution, indiscriminate suppression of microglial function may not be the optimal therapeutic strategy. Future treatments will likely need to shift microglia from a pro-nociceptive to a pro-resolving state, rather than simply depleting them. Conceptually, this parallels cancer immunotherapy, which often seeks to reset immune-cell behavior (eg, checkpoint blockade) rather than merely suppressing or depleting immune cells.

SEX DIFFERENCES IN MICROGLIA AND PAIN

Sex-specificity is among the most reproducible features of microglial contributions to pain.[56] While nerve injury induces microgliosis and activation in both males and females, males rely much more heavily on microglial signaling to drive neuropathic pain.[57 58] Importantly, these are not simply quantitative differences in the same pathway: recent evidence demonstrates that the same upstream cellular trigger can engage entirely distinct effector mechanisms depending on biological sex, with microglia-derived mediators driving pain in males and adaptive immune cells in females via independent molecular routes.[57–59]

Single-cell RNA sequencing of spinal cord microglia after peripheral nerve injury in mice identified a male-specific inflammatory microglial cluster that was largely absent in female mice, in whom microglial transcriptional responses to nerve injury were more muted.[60] Functionally, pharmacologic or chemogenetic inhibition of microglia, or microglial depletion, reliably reverses allodynia in male mice but has little effect in females.[23 58 61]

In males, microglia-dependent pathways are critical: ATP–P2X4/P2X7 signaling and p38 MAPK activation are required for the full expression of neuropathic pain, and inhibition of p38 MAPK reverses allodynia in male but not female mice.[61] In contrast, females recruit adaptive immune mechanisms to mediate and modulate pain behaviors: microglial inhibition does not attenuate allodynia in females, whereas T-cell manipulations do. Regulatory T cells suppress microglial-dependent pain signaling in females, and meningeal regulatory T cells have recently been identified as female-specific modulators of neuropathic pain.[58 59 62 63]

Clinical relevance—toward sex-informed therapeutics

These preclinical findings suggest that microglia-targeted therapies may be more effective in some patient groups than others. At a minimum, they argue for sex-stratified analysis in future trials of microglia-modulating interventions.[56 57]

HUMAN EVIDENCE FOR MICROGLIAL INVOLVEMENT IN PAIN

Several human dorsal root ganglion (DRG) studies bridge preclinical neuroimmune findings and clinical pain. In patients undergoing surgery for radicular pain, electrophysiologic recordings from excised DRG neurons demonstrated spontaneous activity that correlated with pain severity.[64 65] Transcriptomic analysis highlighted immune and plasticity modules overlapping rodent neuropathy models.[64 65] Spatial and bulk transcriptomics of human DRG from patients with chronic pain and painful diabetic neuropathy have likewise revealed upregulation of inflammatory and macrophage-associated genes and loss of specific neuronal populations, echoing themes from animal work on neuroimmune contributions to neuropathic pain.[66] By contrast, direct molecular profiling of human spinal microglia in chronic pain is not yet available, so microglial mechanisms in patients are still inferred from imaging and from animal data rather than measured directly.

Histopathology

Spinal cord biopsies are not feasible except in rare circumstances, and microglia biomarkers are difficult to assess in vivo. Postmortem examination of a patient with long-standing CRPS revealed widespread microglial activation in the dorsal horn throughout the spinal cord.[67] Although anecdotal, this observation aligns with extensive animal data linking microglial activation to chronic pain.

Glial-signal imaging

Positron emission tomography (PET) using radioligands for the 18 kDa translocator protein (TSPO) has provided the most direct, though imperfect, window into glial activation in living patients.[11 12] TSPO is expressed on microglia, astrocytes and other myeloid cells, so the signal is not microglia-specific. Quantitatively, approximately 30%–40% greater radioligand uptake has been reported in the cervical spinal cord and nerve roots of patients with chronic radicular pain compared with healthy controls, with signal intensity correlating with pain severity.[11] Significantly elevated TSPO signal has been found in thalamic and cortical regions of patients with chronic low back pain.[12] Increased TSPO uptake has also been observed in brain regions of individuals with CRPS and fibromyalgia.[68]

More recently, PET ligands targeting CSF1R, which is more restricted to microglia and monocytes than TSPO, have shown promise as more specific markers of microglial activation in neuroinflammatory conditions.[13] Available CSF1R-PET data are limited to feasibility and first-in-human studies; no pain patient cohort data have yet been published.[13] These tools are still in early development but may eventually allow clinicians to visualize microglial activity with greater cellular specificity.

Clinical relevance—imaging as a biomarker

Glial signal PET is not yet ready for routine pain management. Still, it offers a framework for mechanism-based patient selection in early-phase trials of microglia-modulating therapies and for monitoring whether interventions alter microglial activity in humans.

OTHER NEUROIMMUNE CONTRIBUTORS: A BRIEF OVERVIEW

Microglia are not the only neuroimmune contributors to neuropathic pain; peripheral and DRG macrophages, Schwann cells, T cells and other immune cells also contribute to neuropathic pain.[5] Peripheral macrophages at the injury site and in the DRG can release many of the same mediators as microglia (IL-1β, TNFα, IL-6, DAMPs, reactive oxygen species) and communicate bidirectionally with nociceptors.[69] In conditions such as rheumatoid arthritis, osteoarthritis and chemotherapy-induced peripheral neuropathy, macrophage activation correlates with pain severity and, in some cases, has been successfully targeted to prevent or reduce neuropathy.[70] These various cell types form part of a distributed neuroimmune network in which microglia are the CNS representation.

CLINICAL IMPLICATIONS OF MICROGLIAL NEUROIMMUNE INTERACTIONS

Even without microglia-specific therapies, many treatments already used for pain management likely exert at least part of their benefit through the neuroimmune interface, including effects on microglia.[5 71] Although the precise mechanisms of many analgesic interventions remain incompletely defined, appreciating their potential neuroimmune effects may help clinicians think more strategically about timing, patient selection and future therapeutic development.

Steroids

Glucocorticoids are widely used in interventional pain practice, for example, in epidural injections for radicular pain and intra-articular injections for degenerative joint disease. Clinical trials show that steroids can improve pain and function and delay or reduce the need for surgery in some patients.[72] Preclinical studies suggest that steroids suppress peripheral inflammation, reduce spinal cytokine production, dampen microglial activation and decrease neuronal hyperexcitability.[73]

From a microglial perspective, the main considerations are when steroids are given and which pathways they engage. Early, targeted use around the time of nerve injury may have more potent effects on microglial-driven central sensitization than late use in long-standing pain.

Cytokine-targeted biologics

Biologics that neutralize IL-1β, TNFα or IL-6 have transformed the treatment of rheumatoid arthritis and other systemic inflammatory diseases. In small clinical studies, IL-6 receptor blockade produced meaningful relief in discogenic low back pain and refractory radicular symptoms, whereas anti-TNF therapies have shown possible benefit in vertebral disc-related pain but with inconsistent results across studies, limiting broad clinical application.[74 75]

By targeting cytokines central to microglial–neuronal communication, these agents offer proof of concept that selective modulation of neuroimmune pathways can improve pain. However, results have been mixed—pointing to a need for context-specific targeting and better biomarkers to identify those with a neuroimmune-driven pain phenotype.

Anti-NGF monoclonal antibodies illustrate both the promise and the pitfalls of neuroimmune-targeted analgesia. Across multiple randomized trials in hip and knee osteoarthritis, anti-NGF antibodies produced clinically meaningful reductions in pain and improvements in function compared with placebo or standard analgesics.[76] However, treatment was also associated with increased rates of rapidly progressive osteoarthritis, osteonecrosis and joint replacement, leading to regulatory halts or restrictions on the development of this class. Anti-NGF therapies thus illustrate that even tightly mechanism-targeted neuroimmune agents can produce unanticipated consequences at scale.

Glial modulators

As discussed in the 'Microglia Surveillance and the Timing of Neuropathic Pain' section above, minocycline produced robust analgesic effects in rodent neuropathy models but has not translated to reliable clinical benefit. A randomized controlled trial found that minocycline failed to reduce pain in patients with chronic radicular pain, and mechanistic reappraisal suggested that its broad CNS effects, including impacts on mood and gut microbiome, confound interpretation of clinical results and may, in some cases, prolong or worsen pain.[24 25] Its lack of microglial specificity remains the most fundamental limitation.

Propentofylline, which broadly inhibits glial activation and cytokine production, reversed neuropathic pain in preclinical models but failed to show clear benefit in trials for postherpetic neuralgia, CRPS, diabetic neuropathy and migraine.[77]

These experiences do not invalidate microglia as a target; rather, they highlight that non-specific, late, or 'one-size-fits-all' glial inhibition is unlikely to succeed. Future strategies may need to combine more precise pathway targeting with careful timing and patient selection.

Neuromodulation

Neuromodulation therapies such as spinal cord stimulation (SCS) are being used increasingly for conditions including failed back surgery syndrome, CRPS and painful diabetic neuropathy. In animal models, SCS reduces microglial activation and modifies neuroinflammatory gene expression in both neurons and glia.[78] These mechanistic findings are consistent with randomized clinical trial evidence that modern SCS paradigms improve pain and function in chronic low back pain, although direct molecular-clinical correlations in humans remain limited.[79]

Regenerative medicine

Regenerative approaches such as platelet-rich plasma and mesenchymal stromal cell therapies are increasingly used for osteoarthritis, tendinopathies and degenerative spine conditions. Beyond structural repair, these therapies secrete IL-4, IL-10 and specialized pro-resolving mediators that can shift macrophages and possibly microglia towards pro-resolving phenotypes.[71] This approach harnesses the immune system's own resolution programs rather than suppressing them.

A conceptual framework for neuroimmune-informed pain management

Preclinical microglial literature challenges a purely neuron-centric view of neuropathic pain. In our interpretation, this body of evidence suggests several conceptual shifts that may help clinicians reason about neuropathic pain mechanisms, patient selection and future therapeutic development (figure 2).

To organize these principles, we propose a conceptual three-stage framework for neuroimmune-informed pain management

(figure 2), intended as a heuristic for clinical reasoning and trial design rather than a practice guideline. In stage 1 (acute/perioperative, 0–2 weeks), the priority is identifying patients at high risk for developing chronic neuropathic pain and considering whether the timing of anti-inflammatory or neuroimmune-modulating interventions can be optimized to intercept the early microglial activation window. In stage 2 (subacute, 2–12 weeks), when maladaptive central sensitization is consolidating, cytokine-targeted biologics may be most relevant. In stage 3 (chronic, >12 weeks), the therapeutic priority shifts to promoting resolution: resolvin-class mediators, regenerative therapies, neuromodulation and—once validated—CSF1R-PET-guided patient selection and sex-stratified treatment allocation. Across all stages, sex should be considered a potential treatment-effect modifier, and the therapeutic goal should be to reprogram microglial state towards resolution rather than to eliminate microglial function—a distinction critical to both efficacy and safety.

Translating microglial targets into clinical therapies will require careful attention to adverse effects. First, most pathways discussed here (CSF1R, TLR, cytokine receptors, STING) are not CNS-restricted; they are shared with peripheral macrophages and monocytes, raising the risk of systemic immunosuppression and infection. CNS-restricted or intrathecal drug delivery strategies may be necessary to achieve acceptable safety margins. Second, as discussed above, the anti-NGF experience illustrates that even tightly mechanism-targeted neuroimmune agents can produce unanticipated consequences at scale; thorough safety evaluation is required before broad adoption.[76] Third, microglia perform essential homeostatic functions (synaptic pruning, circuit maintenance and debris clearance) that are distinct from their neuroinflammatory roles. Prolonged or non-selective microglial suppression risks impairing these functions, with unknown long-term consequences for CNS plasticity.

CONCLUSIONS

Preclinical and early human data support a central role for microglia in neuropathic pain pathophysiology. Microglia detect danger signals from injured nerves, release cytokines and other mediators that rewire dorsal horn circuits and participate in both the onset and resolution of pain. For clinicians, the value of this preclinical experience lies not in dictating immediate changes in prescribing or procedural choices, but in expanding how we think about neuropathic pain. It suggests that some of our current treatments may succeed or fail, in part, based on how they influence microglial states and points towards a future in which we use precision medicine to target the neuroimmune interface using pathway-specific inhibitors, biologics, neuromodulation and regenerative strategies timed to the corresponding stage of disease.

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