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REVIEW

Beyond inflammation: a comprehensive microglial regulation model in chronic pain

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Abstract

Chronic pain has emerged as a disorder of persistent neuroimmune dysregulation, with microglia playing a pivotal role in shaping maladaptive plasticity. Beyond classical inflammatory pathways, recent discoveries highlight microglial involvement in epigenetic remodeling, metabolic reprogramming, and synaptic modulation. These multidimensional processes sustain microglial activation and promote central sensitization, even in the absence of ongoing peripheral injury. This review proposes a comprehensive framework for understanding microglial regulation in chronic pain, emphasizing the failure of immune tolerance, aberrant neuron–glia signaling, and the emergence of disease-perpetuating microglial states. We further discuss therapeutic strategies aimed at selectively targeting microglial phenotypes, including HDAC inhibitors, metabolic modulators, and pathway-specific antagonists. By integrating mechanistic depth with translational insights, this review reframes microglia not only as inflammatory mediators, but as dynamic regulators whose dysregulation underlies pain chronification.

Keywords Chronic pain · Microglia · Epigenetics · Metabolism · Neuroimmune regulation

Introduction

Chronic pain affects over 20–30% of the global population and represents a major healthcare burden with few effective treatments [1]. Unlike acute pain, which is transient and protective, chronic pain persists beyond tissue healing and reflects a pathological state of neural plasticity. Microglia are the primary immune cells of the central nervous system. They contribute to the development and persistence of chronic pain by modulating synaptic transmission, altering neuronal excitability, and sustaining nociceptive sensitization. Recent studies have revealed that microglia actively drive the development and persistence of chronic pain, rather than merely responding to neuronal cues. Experimental models demonstrate that direct stimulation of spinal microglia can induce pain behaviors in the absence of peripheral injury, highlighting their causal role in pain chronification [2]. Notably, microglia exhibit dual functional phenotypes during injury responses, with early activation contributing to repair and prolonged activation leading to sustained inflammation and neurotoxicity, as shown in models of both traumatic brain injury and autoimmune disorders [3, 4].

Historically, research has focused on the pro-inflammatory functions of microglia. Following peripheral nerve injury, activation of receptors such as Toll-like receptor 4 (TLR4) leads to the release of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and other cytokines that enhance excitatory signaling and suppress inhibition in spinal circuits [5]. While targeting these inflammatory pathways has shown promise in preclinical settings, translation into effective human therapies has been limited. This gap underscores the need for a broader conceptual framework that extends beyond inflammation alone.

Recent discoveries have revealed that microglial function in chronic pain involves epigenetic alterations that imprint a lasting pro-nociceptive phenotype. Modifications such

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as DNA methylation and histone acetylation can reshape microglial gene expression toward heightened responsiveness, even after the initial insult subsides [6]. For instance, recent studies identified transcriptional reprogramming driven by SOX11 and ARID1A in the spinal cord as a key contributor to neuropathic pain persistence [7]. Metabolic shifts, particularly a bias toward aerobic glycolysis and disrupted mitochondrial function, have also been linked to sustained microglial activation and resistance to immune resolution [8]. At the same time, specific subsets of microglia can exert protective or reparative roles. These include populations that secrete neurotrophic and anti-inflammatory factors, or that actively participate in synaptic remodeling to restore homeostasis [9]. Emerging data further show that microglial signaling pathways such as Wnt1–LKB1 play a critical role in curbing pro-inflammatory polarization via autophagy induction, offering a novel avenue for homeostatic rebalancing [10, 11]. Beyond inflammation, recent studies reveal that microglia undergo epigenetic, metabolic, and functional reprogramming that critically shape their role in chronic pain. Activation triggers the enrichment of permissive histone marks (e.g., acetylation of histone H3 at lysine 27, H3K27ac) at promoters and enhancers of immune genes [12–14]. These multidimensional changes—including epigenetic reprogramming, metabolic rewiring, and reparative phenotypes—necessitate a comprehensive model of microglial regulation in chronic pain.

To capture this functional diversity, we advance a multidimensional regulation model of microglial involvement in chronic pain. Rather than being defined solely by inflammatory outputs, microglia are seen as dynamic integrators of molecular, metabolic, and epigenetic cues. Their sustained activation, plasticity, and crosstalk with neurons may collectively determine whether pain resolves or becomes chronic. This review explores the evolving mechanistic understanding of microglial regulation in chronic pain and discusses its implications for the development of next-generation therapeutics. This conceptual framework is summarized in Fig. 1, which outlines the four interdependent regulatory axes—inflammatory receptor signaling, epigenetic regulation, metabolic reprogramming, and immune tolerance & resolution—that collectively shape microglial states and contribute to the persistence or resolution of chronic pain. A side-by-side comparison of microglial states across acute,

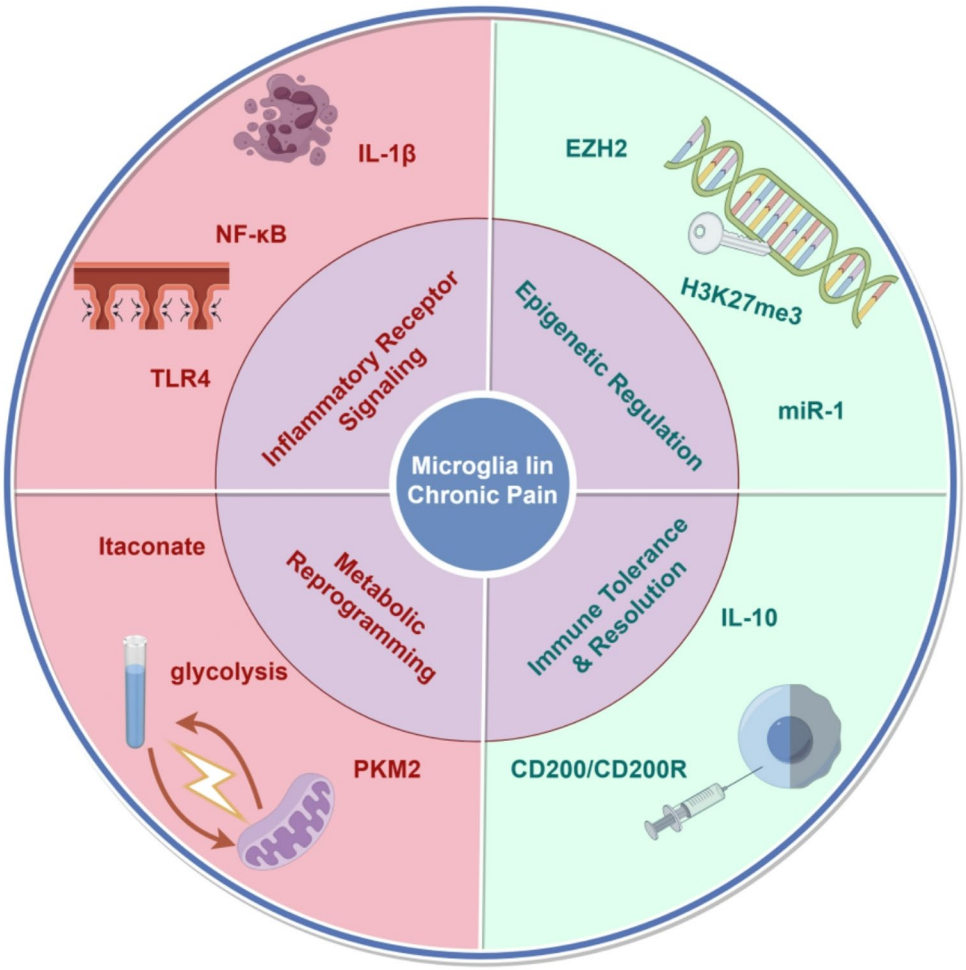

Fig. 1 Multidimensional regulation model of microglial involvement in chronic pain. Microglia integrate signals from four interrelated axes to determine their functional phenotype in chronic pain. (1) Inflammatory receptor signaling (upper left quadrant) is mediated by TLR4–NF-κB pathways driving IL-1β release and sustained neuroinflammation. (2) Epigenetic regulation (upper right) involves repressive modifications (EZH2-mediated H3K27me3) and microRNAs (e.g., miR-1) that shape gene expression programs. (3) Metabolic reprogramming (lower left) includes enhanced glycolysis and PKM2 activity alongside regulatory metabolites like itaconate, supporting an inflammatory state. (4) Immune tolerance and resolution (lower right) are promoted by IL-10, CD200/CD200R signaling, and other pathways that restore homeostasis and resolve inflammation. These axes collectively determine whether microglia adopt a pathogenic or reparative phenotype during the transition from acute to chronic pain

chronic/'trained', and resolution/anti-inflammatory phases is provided in Table 1.

Classical microglial activation mechanisms in chronic pain

Inflammatory receptor signaling and cytokine release

Microglial activation in chronic pain is primarily driven by innate immune signaling. In response to nerve injury or noxious stimuli, microglia transition from a homeostatic surveillant state to a reactive phenotype, marked by the upregulation of pattern-recognition receptors (PRRs), especially Toll-like receptors (TLRs) [15, 16]. TLR4 is particularly crucial in this process, activated by danger-associated molecular patterns (e.g., HMGB1) released from injured nerves, as well as pathogen-associated molecules like LPS in infection-driven pain [17]. TLR4 contributes to the development of mechanical allodynia after nerve injury [18]; therapeutic strategies targeting TLR4 are discussed in the 'Modulating Neuroimmune Signaling Pathways' section.

Neuroimmune sensitization and purinergic signaling

Activated microglia release a cascade of cytokines and chemokines that modulate neuronal activity and synaptic transmission in pain pathways. Classical M1-polarized microglia release IL-1β, TNF-α, and IL-6; together with CCL2, these mediators amplify dorsal horn excitability and maintain a neuroinflammatory milieu [5]. A recent study demonstrated that IL-1β produced by spinal microglia directly contributes to pain hypersensitivity in vivo, reinforcing its role as a driver of chronic pain [2].

Receptor-Mediated signaling and Microglia-Neuron communication

Beyond cytokines, microglia interact with neurons through receptor-mediated signaling, which plays a significant role in pain modulation. Following nerve injury, extracellular ATP activates microglial P2×4, elevating intracellular calcium and p38 MAPK signaling and inducing BDNF release [19, 20]. This P2×4–BDNF pathway is crucial for tactile allodynia, with BDNF-driven downregulation of neuronal KCC2 causing disinhibition [21]. Additionally, microglia communicate with neurons via fractalkine (CX3CL1), which binds to CX3CR1 on microglia, activating them and releasing pro-inflammatory mediators such as IL-1β. Inhibiting CX3CR1 signaling attenuates neuropathic pain, underscoring the importance of neuron–microglia crosstalk in pain maintenance [22, 23].

Limitations of the classical model

While TLR-driven inflammation, cytokine release, and purinergic/fractalkine signaling explain much of the early phase of microglial activation, they do not fully account for the

Table 1 Microglial States across pain phases—features and signatures

Feature	Acute Pro-inflammatory	Chronic Primed (Trained)	Resolution/Anti-inflammatory
Triggers	TLR4 ligands (HMGB1, LPS), ATP (P2×4/7)	Persistent damage signals (e.g., tissue injury), lactate	Neuronal checkpoints (CD200–CD200R), PD-1/PD-L1; anti-inflammatory cytokines (IL-10, TGF-β)
Pathways	NF-κB, MAPKs, NLRP3 inflammasome	Sustained NF-κB, nuclear PKM2 activation, p300-mediated transcription	IL-10R/STAT3, TGF-βR/SMAD, AMPK, NRF2 pathways for anti-inflammatory responses
Cytokines	↑IL-1β, TNF-α, IL-6, CCL2	↑IL-1β, TNF-α, ↓IL-10	↑IL-10, TGF-β, IGF-1 (anti-inflammatory and neuroprotective factors)
Metabolism	↑Glycolysis, ↑lactate, ↓OXPHOS (mitochondrial dysfunction)	Persistent glycolysis, mitochondrial dysfunction, ↓AMPK activity	Restored OXPHOS, ↑Fatty Acid Oxidation (FAO), Itaconate, ↑AMPK activity
Epigenetic Marks	Activating marks (H3K27ac, H3K4me3)	Persistent activating marks, DNA hypomethylation, ↑miR-155	Repressive marks (H3K27me3), DNA remethylation, ↑miR-124/miR-146a (anti-inflammatory miRNAs)
Functions	Sensitizes pain circuits	Maintains pain hypersensitivity	Resolves pain, restores homeostasis, neuroprotection

"Primed/Trained" denotes a persistent pro-inflammatory microglial program beyond the initial trigger. "↑/↓" indicate relative increase/decrease versus basal. Abbreviations: BDNF, brain-derived neurotrophic factor; CX3CL1, fractalkine; CX3CR1, fractalkine receptor; HIF-1α, hypoxia-inducible factor-1α; HMGB1, high-mobility group box 1; IL-1β, interleukin-1β; IL-10R, interleukin-10 receptor; KCC2, K-Cl cotransporter 2; OXPHOS, oxidative phosphorylation; FAO, fatty-acid oxidation; PKM2, pyruvate kinase M2; STAT3, signal transducer and activator of transcription 3; AMPK, AMP-activated protein kinase; NRF2, nuclear factor erythroid 2–related factor 2; miR, microRNA

persistence of chronic pain. Blocking individual cytokines or receptors often yields partial analgesic effects, as microglia can compensate by upregulating alternative inflammatory pathways. Additionally, these inflammatory pathways are transient, yet chronic pain persists for years, suggesting molecular memory in microglia. Recent studies indicate that following nerve injury, microglia acquire lasting transcriptional changes consistent with a primed state that may underlie chronic pain hypersensitivity [24]. Moreover, the classical M1/M2 polarization model is overly simplistic, as microglial functions evolve dynamically throughout chronic pain. Some microglial subsets, such as those arising in the resolution phase, promote pain remission through the release of insulin-like growth factor-1 (IGF-1), an anti-inflammatory and neuroprotective factor [14, 25]. These findings illustrate that microglia exhibit context-dependent actions that evolve over time, emphasizing the need for a more comprehensive model. Furthermore, metabolic reprogramming and immune resolution failure significantly contribute to chronic pain maintenance, areas not fully addressed by the classical pathways. If microglia remain in a persistently activated state due to metabolic dysfunction or inadequate resolution signals, neuroinflammation and pain will persist. Sex differences in microglial signaling are increasingly recognized, with studies showing that TLR4- and P2 × 4 receptor–dependent mechanisms contribute more prominently to neuropathic pain in males than in females [26, 27]. These differences may influence the efficacy of microglia-targeted therapies, underscoring the importance of including sex as a biological variable in preclinical and clinical studies. Classical mechanisms—TLR activation, cytokines, and purinergic signaling—explain the initiation of microglial activation. They do not, however, account for pain chronification. This gap motivates a broader view that emphasizes epigenetic reprogramming, metabolic shifts, and dysregulated resolution, which we discuss in the following sections.

Chromatin-level and transcriptional regulation (Epigenetics)

Histone modifications and microglial "inflammatory memory"

Microglial inflammatory memory associates with metabolism-linked histone modifications without elaborating specific marks here [28]. This chromatin remodeling establishes an "innate memory" that primes microglia for exaggerated responses upon re-stimulation. For example, CBP/p300-mediated H3K27 acetylation has been shown to regulate the transcription of inflammatory effectors such as iNOS in myeloid cells, suggesting a potential mechanism for epigenetic memory in response to stimuli like TLR ligands [29]. Repressive histone modifications such as H3K27me3, typically catalyzed by Polycomb complexes, are known to constrain inflammatory gene expression in myeloid cells; loss of these marks has been implicated in dysregulated immune responses in disease contexts [29].

In neuropathic pain models, injury-induced histone modifications have been directly linked to persistent glial activation. For instance, peripheral nerve trauma increases histone acetylation at promoters of chemokine genes (CCL2/3 and CXCL1/2) in spinal microglia, driving their overexpression. Inhibiting histone acetyltransferases such as p300/CBP suppresses the expression of pain-related genes like BDNF and COX-2, thereby alleviating neuropathic pain [30]. After nerve injury, dorsal horn microglia exhibit increased HDAC1 expression and concomitant hypoacetylation of histone H3K9, correlating with mechanical allodynia; interventions that reduce HDAC1 levels or enhance H3K9 acetylation—such as exercise—attenuate these pain behaviors [31]. Overall, these findings show that histone modifications serve as pivotal regulators of microglial state, encoding an epigenetic "fingerprint" of past inflammatory events that can sustain chronic pain pathology.

DNA methylation and sustained microglial priming

Beyond histone marks, covalent DNA modifications such as DNA methylation also contribute to long-term transcriptional reprogramming in chronic pain. DNA methylation (the addition of methyl groups to CpG sites) generally represses gene expression and can lock microglia into persistent pro- or anti-inflammatory phenotypes. After nerve injury, DNA methyltransferases (DNMT1 and DNMT3) and methyl-CpG-binding protein 2 (MeCP2) are upregulated in the spinal cord, correlating with the repression of certain anti-nociceptive genes [32, 33]. Pharmacological blockade of DNA methylation can reactivate these genes and mitigate pain. For instance, systemic 5-azacytidine (a DNMT inhibitor) reversed nerve injury–induced hyperalgesia, presumably by de-methylating and re-expressing silenced analgesic pathways [33]. MeCP2, a methyl-DNA binding protein that recruits HDACs, regulates immune gene expression in microglia in response to inflammatory stimuli, though its specific contribution to neuropathic pain maintenance following nerve injury remains to be fully elucidated [34]. Notably, inhibiting DNMTs or MeCP2 not only reactivates gene expression but also reduces microglia-driven cytokine release.

Paradoxically, a loss of DNA methylation can also facilitate pain chronicity by de-repressing pro-inflammatory genes. For example, spinal nerve ligation downregulates

DNMT3b, leading to hypomethylation of the Cxcr3 chemokine receptor gene in dorsal horn neurons and aberrant CXCR3 overexpression; this contributes to central sensitization and pain, which can be relieved by blocking CXCR3 signaling [35]. These examples illustrate that aberrant DNA methylation patterns – whether excessive or insufficient – can encode a "primed" state in microglia and pain pathways. Through DNA methylation, microglia effectively retain a biochemical memory of past insults, altering their baseline transcriptional set-point (e.g., lowering the threshold for cytokine gene induction) long after the inciting injury. Such epigenetic priming is thought to be a key mechanism whereby early-life inflammatory or stressful events predispose individuals to heightened pain sensitivity later in life. Importantly, because DNA methylation is enzymatically reversible, epigenetic drugs targeting DNMTs or methyl-binding repressors are being explored to "reset" maladaptive microglial programming in chronic pain.

microRNA-mediated regulation of microglial activation

MicroRNAs (miRNAs) provide a third layer of epigenetic control in chronic pain. These ~22-nucleotide non-coding RNAs fine-tune gene expression post-transcriptionally and can stably alter cellular phenotypes long after an insult. Microglia express a repertoire of miRNAs that regulate inflammatory polarization, and persistent shifts in miRNA expression have been linked to chronic pain states [36, 37]. One example is microRNA-124 (miR-124), a microglia-enriched regulator that maintains a homeostatic phenotype. In chronic neuroinflammation and pain, its downregulation in spinal microglia is associated with a shift toward a pro-inflammatory profile [38]. In preclinical models, loss of miR-124 (e.g., in GRK2-deficient mice) permits M1-skewed activation with excess cytokine production and prolonged hyperalgesia [36]. Conversely, restoring miR-124 levels via intrathecal delivery induces an anti-inflammatory (M2-like) phenotype, suppresses microglial pro-inflammatory markers, and alleviates hyperalgesia [36].

In contrast to miR-124, microRNA-155 (miR-155) exemplifies an inflammation-promoting miRNA that is upregulated in activated microglia. MiR-155 targets negative regulators of immune signaling, so its elevation sustains pathways like NF-κB and the NLRP3 inflammasome. In chronic pain conditions, spinal miR-155-5p is significantly elevated in microglia and contributes to neuroinflammation and pain hypersensitivity [39]. Inhibiting miR-155 (using antagomirs or genetic knockout) attenuates neuropathic pain behaviors and dampens microglial release of pro-inflammatory mediators [40].

Beyond these two examples, many other miRNAs orchestrate microglial responses relevant to pain. For instance, miR-146a acts as a feedback suppressor of Toll-like receptor signaling, restraining excessive cytokine induction; the net balance of such miRNA networks after injury helps determine whether microglia resolve inflammation or become chronically primed [41]. Notably, microglia-derived miRNAs can also transfer between cells (e.g., via exosomes), propagating neuroinflammatory or even protective signals to neighboring neurons and astrocytes [37, 42]. Consistent with their importance, profiling studies have identified miR-124 and miR-155 among the pivotal regulators in neuropathic pain. In summary, microRNAs provide a flexible, multilayered mechanism for modulating microglial gene expression, and their dysregulation in chronic pain reinforces the persistent inflammatory bias established by chromatin marks. Therapeutically, specific miRNAs such as miR-99b-3p may serve as targets: replenishment of miR-99b-3p in neuropathic pain models reprograms inflammatory microglia, suppresses NLRP3-dependent pyroptosis, enhances autophagy, and alleviates established pain behaviors—demonstrating the potential to restore microglial homeostasis even after chronic pain is established [43]. These epigenetic layers—including histone modifications, DNA methylation, and microRNA activity—converge to orchestrate microglial transcriptional programs that influence inflammatory output and pain outcomes. Figure 2 summarizes how these regulatory mechanisms integrate to shape the expression of pro- or anti-inflammatory genes, ultimately determining whether microglia contribute to pain resolution or maintenance.

Metabolic reprogramming in microglia

The glycolytic shift in activated microglia

An emerging paradigm in chronic pain research is that microglia undergo metabolic reprogramming when shifting from a homeostatic to an activated, pro-inflammatory state [44, 45]. In their resting state, microglia primarily rely on mitochondrial oxidative phosphorylation (OXPHOS) to meet basal energy demands. Following peripheral nerve injury, microglia shift their metabolism from oxidative phosphorylation toward glycolysis, supporting a pro-inflammatory phenotype [46, 47]. This metabolic transition involves enhanced glucose uptake and conversion of pyruvate to lactate even under normoxic conditions. Although glycolysis yields less ATP, it delivers energy quickly. It also provides biosynthetic intermediates for proliferation and for the synthesis of inflammatory mediators [48]. In neuropathic pain models, this shift toward glycolysis and away

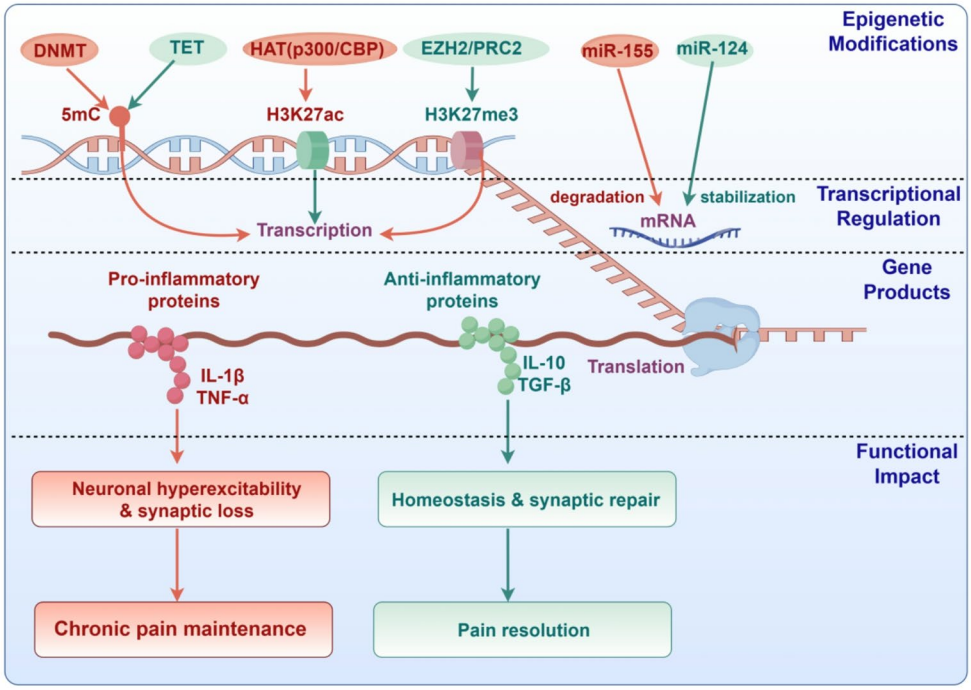

Fig. 2 Epigenetic control of microglial transcription and its functional consequences in chronic pain. DNA methylation (5mC) by DNMT represses gene transcription, while TET promotes demethylation. Histone acetylation (e.g., H3K27ac by HAT/p300/CBP) enables chromatin opening and gene expression, whereas trimethylation (H3K27me3 by EZH2/PRC2) induces chromatin condensation and transcriptional silencing. Post-transcriptionally, miR-124 stabilizes mRNAs encoding anti-inflammatory mediators (e.g., IL-10, TGF-β), while miR-155 promotes degradation of transcripts related to resolution. These coordinated layers shape the microglial protein output—favoring either pro-inflammatory cytokines (IL-1β, TNF-α) that drive synaptic loss and pain persistence, or anti-inflammatory factors that support repair and pain resolution. Red arrows indicate inhibitory or pro-inflammatory actions; green arrows indicate activating or anti-inflammatory actions

from mitochondrial respiration has been observed in spinal microglia and is associated with enhanced pro-inflammatory phenotypes and pain hypersensitivity [44, 48]. Together, these findings suggest that metabolic remodeling may reinforce glial activation and contribute to sustained neuroinflammation during chronic pain.

Mechanistically, a glycolytic shift is orchestrated by HIF-1α and key metabolic enzymes. A central regulator is pyruvate kinase M2 (PKM2), an isozyme enriched in immune and glial cells. PKM2 catalyzes the final step of glycolysis and, in its dimeric state, biases pyruvate toward lactate rather than oxidative metabolism. Peripheral nerve injury upregulates spinal PKM2, with expression in neurons, astrocytes, and microglia. Functionally, intrathecal PKM2 siRNA suppresses spinal lactate and IL-1β/TNF-α, reduces p-ERK/p-STAT3, and reverses CCI-induced mechanical allodynia and thermal hyperalgesia, linking glycolytic bias and ERK/STAT3-dependent transcriptional programs to nociceptive hypersensitivity [48].

Overall, the glycolysis-centric metabolism of primed microglia supports their pathogenic output in chronic pain. This shift supplies abundant lactate and ATP: ATP acts as a neurotransmitter that fuels pain signaling (via P2X purinergic receptors), and lactate serves both as an energy substrate for neurons and as a signaling molecule in neuron–glia crosstalk. Notably, high lactate levels have been detected in tissues during chronic neuroinflammatory states, and microglial glycolysis is increasingly recognized not only as a consequence of activation but also as a contributor to pain propagation by altering the tissue microenvironment [48, 49].

Lactate signaling and histone lactylation

Activated microglia undergoing a glycolytic shift release excess lactate, which functions as a local signaling molecule in the CNS. Extracellular lactate engages G-protein–coupled receptors on neurons and glia or serves as a metabolic substrate [50]. Elevated lactate provokes microglia and astrocytes to secrete TNF-α, IL-6, and IL-1β, amplifying neuroinflammation.

In dorsal root ganglion (DRG) neurons after peripheral nerve injury, lactate drives histone lactylation at H3K18 and H4K12 via the lactyltransferase p300, linking glycolysis to pronociceptive gene expression [51]. Histone lactylation can upregulate transcription in a context-dependent manner. In microglia, excess lactate increases histone lysine lactylation and sustains pro-inflammatory gene programs.

Disease models demonstrate that microglial H3K9 lactylation increases alongside enhanced expression of targets such as Slc7a11. In neuropathic pain, microglial glycolytic upshift increases lactate and protein/histone lactylation; microglial CMPK2 promotes glycolysis-driven lactylation that deactivates cGAS–STING signaling and facilitates pain sensitization, and targeting CMPK2 attenuates allodynia [52]. Concordantly, in sensory neurons histone H4K8/H4K12 lactylation increases across multiple pain models and causally regulates heat nociception via DOCK4–Nav1.7 trafficking [53]. Conversely, glycolysis blockade with 2-deoxyglucose reduces both lactate and histone lactylation, underscoring the pathological relevance of the lactate–lactylation axis [54]. Although pain-specific evidence remains preliminary, studies in neurodegeneration implicate lactylation in persistent microglial activation [55, 56]. These examples demonstrate how a buildup of lactate can reinforce the epigenetic and transcriptional programs of "trained" microglia.

Dynamic regulation of lactate and histone lactylation is documented in the injured spinal cord; microglial H4K12 lactylation increases after SCI. However, whether lactylation redirects transcription toward reparative programs during resolution of chronic pain remains unproven [57]. Pharmacologically lowering spinal lactate with intrathecal LDHA inhibitors (FX11, oxamate) alleviates mechanical allodynia and thermal hyperalgesia in CCI rats and concomitantly dampens neuroinflammation [58]. Consistent with this, pharmacological disruption of lactylation—for instance, using a p300 inhibitor—has been shown to blunt the lactate-induced "training" effect in microglia [59, 60]. Beyond microglia themselves, lactate released by these cells can also affect neurons. In a neuropathic pain model, microglia-derived lactate entered sensory neurons and induced histone lactylation in neuronal chromatin, upregulating pro-nociceptive genes (including those encoding pain-facilitating receptors) [46, 55, 61]. This finding adds a new dimension to neuron–glia interactions in chronic pain.

In summary, excess lactate is both a marker and a maker of persistent microglial activation. By serving as a substrate for chromatin modification (lactylation), lactate endows microglia—and even neighboring cells—with a lasting inflammatory drive. Therapeutic approaches that reduce CNS lactate levels (for example, by promoting its utilization in mitochondria or inhibiting its production) may therefore not only deprive microglia of a fermentative fuel but also erase the lactylation-based "inflammatory memory" that sustains chronic pain.

Resolution-linked metabolic programs (OXPHOS, itaconate, AMPK)

Encouragingly, the metabolic flexibility that enables microglial hyperactivation also provides opportunities to terminate inflammation and promote resolution. As acute injury transitions to healing, microglia typically undergo a metabolic rerouting opposite to the Warburg effect—returning to mitochondrial oxidative phosphorylation, increasing fatty acid oxidation, and engaging anti-inflammatory metabolic programs [62].

A key immunometabolic "brake" in this process is the production of itaconate, a metabolite derived from the tricarboxylic acid (TCA) cycle. Activated microglia induce the enzyme IRG1 (also known as ACOD1) to convert cis-aconitate into itaconate. Although itaconate accumulates only after initial pro-inflammatory signaling, it plays a crucial role in shutting down inflammation. Itaconate and its derivatives suppress microglial activation via multiple mechanisms: (i) itaconate competitively inhibits succinate dehydrogenase, leading to succinate accumulation and stabilization of HIF-1α (which paradoxically creates negative feedback on pro–IL-1β production); (ii) itaconate alkylates cysteine residues on key inflammatory proteins (including NLRP3 and KEAP1), thereby inhibiting inflammasome assembly and activating the anti-oxidant transcription factor NRF2 [63, 64]. Consistent with this, knockdown of Acod1 in LPS-activated microglia exacerbates neuroinflammation and neuronal dysfunction, whereas treatment with 4-octyl itaconate (a cell-permeable itaconate derivative) inhibits microglial activation and ameliorates inflammation-induced symptoms [63]. These findings highlight itaconate as a natural resolution metabolite that helps microglia exit the M1 state.

Microglial energy-sensing pathways are also pivotal in determining their inflammatory or reparative phenotype. Chief among these is AMP-activated protein kinase (AMPK), a cellular "fuel gauge" activated by an elevated AMP/ATP ratio. During the rodent recovery phase or under metabolic stress, AMPK becomes active in microglia and orchestrates a broad anti-inflammatory program [65]. Activated AMPK promotes catabolic metabolism—enhancing β-oxidation of fatty acids and mitochondrial ATP production—while concurrently inhibiting anabolic and inflammatory pathways [66]. The net effect is restoration of cellular energy balance and a shift of microglia from an aggressive M1 state toward a more restorative phenotype. AMPK activation induces autophagy, including mitophagy, primarily by inhibiting mTORC1 and phosphorylating ULK1, which promotes the clearance of damaged mitochondria and contributes to inflammation resolution by limiting IL-1β and TNF-α production [67, 68].

In chronic pain conditions, however, persistent inflammatory stimuli often keep AMPK activity suppressed, removing this metabolic brake on microglia. Studies in models of Alzheimer's disease and systemic inflammation have shown microglial NLRP3 inflammasome activation and sustained proinflammatory cytokine release via NF-κB-driven signaling [69, 70]. Conversely, pharmacological activation of AMPK exerts anti-inflammatory effects in microglia. For example, in male mice the diabetes drug metformin activates AMPK in spinal cord microglia and prevents or reverses neuropathic pain, accompanied by reduced microglial activation in vivo [71].

Improved mitochondrial function is another hallmark of resolving microglia. As they resume OXPHOS, microglia increase their spare respiratory capacity and rely on an efficient electron transport chain, including enhanced activity of the mitochondrial complex I pathway [72]. Conversely, excessive ROS generated during chronic microglial activation contributes to a sustained neuroinflammatory state, and antioxidant interventions targeting mitochondrial ROS can attenuate this response [73]. Collectively, while glycolysis and its byproducts anchor microglia in a primed, pain-promoting state, engaging OXPHOS and other anti-inflammatory metabolic pathways is central to microglial de-priming. By activating sensors like AMPK and generating metabolites such as itaconate, microglia can be guided back to a homeostatic state that supports tissue repair and pain resolution. Targeting these metabolic hubs offers a compelling approach to reprogram maladaptive microglia in chronic pain – effectively shifting the microglial regulatory paradigm "beyond inflammation" to include restoration of metabolic balance as a cornerstone of therapy. These concepts are illustrated in Fig. 3, which schematically summarizes the metabolic states of microglia and their associated signaling pathways in homeostatic versus activated conditions.

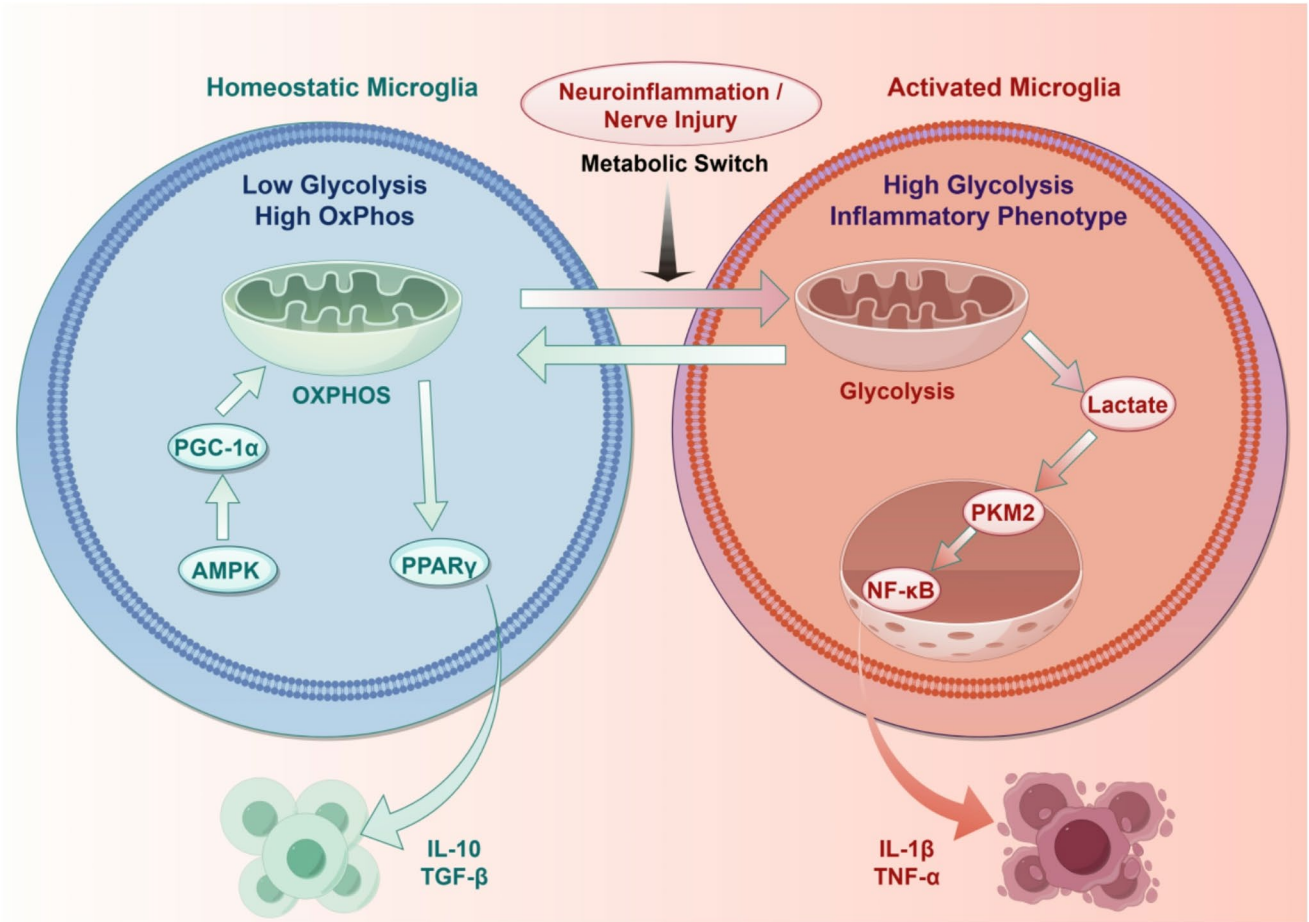

Fig. 3 Immunometabolic states of microglia in chronic pain. Under homeostatic conditions, microglia exhibit low glycolysis and high oxidative phosphorylation (OXPHOS), driven by AMPK and PGC-1α, and activate PPARγ to promote anti-inflammatory cytokines (IL-10, TGF-β). Upon neuroinflammation or nerve injury, microglia switch to a glycolytic, inflammatory phenotype characterized by elevated PKM2, lactate production, NF-κB activation, and secretion of pro-inflammatory cytokines (IL-1β, TNF-α). The figure highlights key molecular mediators in this metabolic transition and their impact on microglial function

Immune tolerance and neuron–microglia interactions

Immune tolerance in microglial activation

Under normal conditions, the CNS maintains microglia in a quiescent, "tolerant" state through inhibitory immune signals. Neuronal expression of CD200 and CX3CL1 ligands engages microglial receptors (CD200R and CX3CR1) to suppress activation, functioning as immune "checkpoints" in mouse models of Parkinson's disease [74]. CD200R activation recruits phosphatases (SHP-1/2) that inhibit NF-κB signaling, promoting an anti-inflammatory phenotype by upregulating IL-10 and TGF-β, key factors for homeostasis. Disruption of this axis, such as the loss of CD200 after nerve injury, removes this restraint, driving microglial polarization toward a pro-inflammatory state (M1-like), which sustains neuroinflammation [75].

IL-10, a key anti-inflammatory cytokine, maintains immune tolerance by suppressing microglial activation and limiting pro-inflammatory cytokine production [76]. Therapeutic augmentation of IL-10 is discussed in the 'Modulating Neuroimmune Signaling Pathways' section. Similarly, in vitro studies show that TGF-β1 can suppress microglial inflammatory triggers and lipid droplet accumulation, promoting an anti-inflammatory (M2-like) profile under stroke-related stress conditions [77].

Chronic pain states may involve impaired tolerance mechanisms or microglial "desensitization," leading to persistent activation. Furthermore, immune checkpoint pathways, such as the PD-1/PD-L1 axis, play a key role in regulating microglial function. Activation of PD-1 by PD-L1 reduces microglial proliferation and inflammation [78]. Enhancing PD-1 signaling in the spinal cord has been shown to reduce microglial activation, alleviating neuropathic pain [79, 80]. In contrast, blocking PD-1 (as with certain immunotherapies) may exacerbate pain by disinhibiting microglia [81].

Together, these findings emphasize that maintaining immune tolerance via neuron–microglia interactions (e.g., CD200–CD200R, PD-1/PD-L1) and anti-inflammatory mediators (IL-10, TGF-β) is crucial for preventing excessive microglial activation. Disruption of these pathways in chronic pain contributes to pain chronification through sustained microglial reactivity.

Bidirectional neuron–microglia signaling

Chronic pain is increasingly understood as a neuroimmune disorder, where maladaptive bidirectional communication between neurons and microglia plays a central role. In chronic pain pathways, neuron-derived fractalkine (CX3CL1) engages microglial CX3CR1 and activates downstream signaling (e.g., p38 MAPK/ERK), promoting microglial activation and synaptic disinhibition. CX3CL1–CX3CR1 signaling sustains microglial reactivity and contributes to mechanical allodynia [82]. Blocking this axis with neutralizing antibodies reduces microglial activation and pain hypersensitivity in preclinical models, highlighting its role in chronic pain maintenance [83].

A crucial mechanism of neuron–microglia communication involves purinergic signaling. The ATP–P2 × 4–BDNF axis (see Sect. Receptor-Mediated signaling and Microglia-Neuron communication) exemplifies neuron–microglia signaling that drives synaptic disinhibition. In addition, P2 × 7 receptor activation leads to inflammasome formation and IL-1β release, which enhances excitatory synaptic currents and amplifies nociceptive signaling, further driving central sensitization.

Another key mechanism of microglia-neuron interaction involves the complement system. In chronic pain, aberrant activation of complement components like C1q and C3 by microglia contributes to synaptic remodeling. Microglia preferentially phagocytose inhibitory synapses in the dorsal horn during neuropathic pain, a process driven by complement receptors such as CR3 [84]. Inhibiting complement activation or C1q protects against synaptic loss and reduces pain hypersensitivity, confirming the role of complement-mediated microglial pruning in pain chronicization [85].

In conclusion, chronic pain is driven by a series of bidirectional signals: neurons release distress signals (e.g., CX3CL1, ATP) to activate microglia, and in turn, microglia secrete BDNF, IL-1β, TNF-α, and complement proteins, leading to synaptic changes and neuronal hyperexcitability. These interactions underlie central sensitization and emphasize the potential of targeting neuron–microglia signaling pathways for therapeutic intervention in chronic pain.

Therapeutic strategies targeting microglial regulation in chronic pain

Epigenetic reprogramming of microglia

One approach to alleviate chronic pain is to "reset" microglia toward a pro-resolving (anti-inflammatory) state by altering their gene expression. The histone deacetylase inhibitor SAHA (vorinostat) alleviates bone cancer pain in rats by suppressing glial activation in the spinal dorsal horn and dorsal root ganglia [86]. Similarly, the selective HDAC6 inhibitor ACY-1215 (ricolinostat) attenuates neuropathic pain and associated comorbidities in peripheral nerve injury models through modulation of neuroinflammation [87]. These studies underscore the epigenetic plasticity of microglia: pharmacologically blocking HDACs shifts microglia away from

Table 2 Therapeutic strategies targeting microglial mechanisms in chronic pain

Strategy	Target/Pathway	Evidence stage	Targeting Scope
SAHA/vorinostat	HDAC inhibition	Preclinical	Systemic
ACY-1215	HDAC6 inhibition	Preclinical	Systemic
Metformin	AMPK activation; microglial metabolic reprogramming	Preclinical	Systemic
2-DG	Glycolysis inhibition	Preclinical	Systemic
IL-10 gene therapy	IL-10R signaling; anti-inflammatory	Preclinical	Local (intrathecal)
TLR4 antagonists	TLR4 inhibition on spinal microglia	Preclinical	Local (intrathecal)
CX3CR1-targeted PLGA nanoparticles	CX3CR1-directed delivery to microglia	Preclinical	Microglia-targeted
CX3CL1–CX3CR1 blockade	CX3CL1–CX3CR1 signaling blockade	Preclinical	Microglia-targeted
Complement C1q inhibition	Complement C1q-mediated synaptic pruning inhibition	Preclinical	Systemic
P2 × 7 receptor antagonists	Purinergic signaling blockade	Preclinical	Systemic
Minocycline	Broad glial inhibition	Clinical Trial	Systemic

"Microglia-targeted" denotes predominant action on microglia (e.g., CX3CR1-directed delivery) and does not imply absolute exclusivity; non-microglial exposure can occur with non-directed delivery. Abbreviations: 2-DG, 2-deoxy-D-glucose; AMPK, AMP-activated protein kinase; BBB, blood–brain barrier; HDAC, histone deacetylase; IL-10, interleukin-10; PLGA, poly(lactic-co-glycolic acid); TLR4, Toll-like receptor 4; CX3CL1, fractalkine; CX3CR1, fractalkine receptor; C1q, complement component 1q

a chronic inflammatory phenotype, suppressing cytokine transcription and promoting pain relief [86, 87]. In essence, epigenetic drugs can reprogram microglial transcriptional programs to dampen neuroinflammation and restore homeostasis in the injured nervous system.

Metabolic reprogramming of microglia

Chronic pain is associated with a metabolic shift in microglia toward a glycolytic (Warburg-like) state that reinforces inflammation. Therapies that reverse this shift – by activating oxidative metabolism or inhibiting glycolysis – can normalize microglial function and reduce pain. For example, the diabetes drug metformin activates AMP-activated protein kinase (AMPK) and was found to prevent or reverse neuropathic pain in rodent models [71]. Metformin's benefit coincided with decreased microglial activation markers (Iba-1) in the spinal cord, suggesting it restores energy balance and reduces neuroinflammation. Conversely, applying the glycolysis inhibitor 2-deoxy-D-glucose (2-DG) in pain models suppressed microglial pro-inflammatory outputs and alleviated pain behaviors [88]. In a mouse bone cancer pain model, intrathecal 2-DG shifted microglia from an M1 (pro-inflammatory) to an M2 (anti-inflammatory) phenotype, reducing TNF-α, IL-1β and IL-6 release while increasing IL-10 [89]. Together, these findings indicate that shifting microglial metabolism away from glycolysis and toward oxidative phosphorylation can curb their pathogenic, pain-promoting activity.

Modulating neuroimmune signaling pathways

Another set of strategies targets the signaling between neurons and microglia in the neuroimmune network. Spinal delivery of IL-10 via non-viral vectors produces long-lasting analgesia in neuropathic models and suppresses microglial cytokine production [90]. Blocking pro-inflammatory cytokine signaling—such as IL-1 receptor, TNF-α, or IL-6 pathways—reduces microglial activation and pain behaviors in preclinical models. Intrathecal TLR4 antagonists (e.g., LPS-RS, FP-1, (+)-naloxone) rapidly reverse established mechanical allodynia in nerve injury and arthritis models [91]. For therapeutic implications of TLR4 inhibition, see the 'Modulating Neuroimmune Signaling Pathways' section. Similarly, disrupting the fractalkine signaling axis (neuronal CX3CL1 to microglial CX3CR1) attenuates pain: mice lacking CX3CR1 exhibit blunted microglial p38-MAPK activation and show significantly less thermal hyperalgesia and mechanical allodynia after nerve injury [92]. In practice, pharmacological or genetic blockade of CX3CL1/CX3CR1 signaling can thus reduce microglial activation and neuropathic pain [22].

Finally, inhibiting the complement cascade in the spinal cord protects synapses from microglial pruning. A recent study showed that blocking complement protein C1q prevents loss of inhibitory synapses in the dorsal horn and substantially attenuates neuropathic pain [85]. In summary, therapies that tip the balance toward anti-inflammatory signals (e.g. IL-10) and/or block key pro-inflammatory microglial pathways (TLR4, fractalkine, complement) can disrupt neuron–glia crosstalk and relieve pain. To provide a structured overview of current intervention pipelines, a summary Table 2 has been compiled to integrate mechanistic targets, evidence maturity, and cellular selectivity of representative microglia-modulating strategies. This synthesis is intended to facilitate comparative appraisal of translational readiness and therapeutic precision.

Translational advances and clinical perspectives

Several microglia-targeted approaches are advancing toward human trials, though results have so far been mixed. The antibiotic minocycline – a non-specific microglial inhibitor – showed only modest efficacy in neuropathic pain trials. A recent review of human studies found that roughly half of trials reported any pain reduction with minocycline, and benefits were generally small [93]. This underscores the need for more specific targets than broad glial suppression. Encouragingly, antagonists of the microglial P2 × 7 receptor (a purinergic receptor involved in inflammasome activation) have shown robust analgesia in animals [94]. Similarly, repurposed drugs that modulate microglia are under investigation: metformin has shown anti-inflammatory effects on microglia in demyelination models and is being evaluated for chronic pain in other settings [95]. Gene therapy approaches (e.g. IL-10 delivery) and biologics targeting microglial cytokines are also in preclinical pipelines. These efforts aim to translate the concept of "microglial reprogramming" into practical pain treatments. A summary of key therapeutic strategies targeting microglial regulation, along with their mechanisms and experimental/clinical evidence, is presented in Table 2 to provide a concise reference for future research and clinical translation.

Challenges and future directions

Despite the promise of microglia-directed therapies, several hurdles remain. Most proposed targets (TLR4, HDAC isoforms, AMPK, etc.) are expressed in many cell types, raising safety and off-target concerns. Moreover, microglia are heterogeneous both regionally and over time in pain states [85]. Microglia play beneficial roles in debris clearance, synaptic maintenance and repair, and indiscriminate suppression could impair these functions. For example, certain levels of TLR4 signaling are needed for myelin debris clearance and nerve repair, and complement-driven pruning is important for spinal cord remodeling after injury [85, 96]. Thus, future therapies will need precision: targeted delivery to the CNS (e.g. via viral vectors or nanoparticles) and biomarkers to identify "pain-driving" microglial states. Ultimately, by tailoring interventions to pathological microglial subtypes while preserving homeostatic cells, these strategies could break the neuroimmune feedback loop of chronic pain and achieve lasting analgesia.

Conclusion and future outlook

In summary, chronic pain can be understood as a state of dysfunctional microglial regulation that perpetuates nociceptive signaling. This review outlined how initial injury signals (e.g. damage-associated molecular patterns activating TLR4 and ATP-driven purinergic signaling) trigger microglial cytokine release and neuronal sensitization, but also how long-term changes—epigenetic "inflammatory memory," metabolic shifts, and failed resolution mechanisms—sustain microglia in a pathogenic state. Microglia–neuron interactions (such as fractalkine–CX3CR1 signaling and complement-mediated synapse loss) further amplify nociceptive transmission, while the absence of adequate anti-inflammatory signals (e.g. insufficient IL-10 or other reparative factors) prevents resolution [82, 97]. Together, these insights form a microglial regulation model of chronic pain, in which persistent alterations in microglial state—not just acute inflammation—drive pain chronification.

For future research and clinical translation, several priorities emerge. One priority is to delineate microglial phenotypes in chronic pain. Advanced tools—such as single-cell transcriptomics and in vivo imaging—can identify pathogenic subsets to target. Another priority is to develop microglia-specific delivery. Blood–brain barrier-permeant nanoparticles or gene vectors can focus drug action on CNS microglia and limit systemic effects [98]. In parallel, incorporating biomarkers of microglial activation into clinical trials (for example, PET ligands for microglial receptors or cerebrospinal fluid cytokine profiles) would enable real-time monitoring of target engagement and treatment efficacy [98].

It will also be important to account for patient heterogeneity in microglia-targeted approaches. Factors like sex, age, and immune background can influence microglial contributions to pain, so future trials should stratify patients or tailor interventions accordingly [99]. Ongoing translation of promising interventions (such as IL-10 gene therapy, metabolic modulators, and P2 × 7 antagonists) with these considerations in mind will help validate the microglia-centric approach in the clinic. By addressing these priorities, microglia-targeted therapies could move from bench to bedside, offering not only improved symptom control but potentially modifying the trajectory of chronic pain. Ultimately, a precision medicine paradigm focused on normalizing microglial function holds promise to break the vicious neuroimmune cycle and provide durable relief for patients with chronic pain.

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Declarations

Competing interests The authors declare no competing interests.

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