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REVIEW

Pulsed Radiofrequency and Epigenetic Modulation of Pain Pathways: A Systematic Review Based on Preclinical Evidence

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Background: Pulsed radiofrequency (PRF) is used for refractory neuropathic pain, yet its mechanisms remain incompletely defined. The dorsal root ganglion (DRG) and peripheral nerves (eg, sciatic nerve) are common targets and key nodes in nociceptive transmission and neuro-immune crosstalk. Compared with implantable electrical neuromodulation (SCS/PNS), PRF provides non-invasive, percutaneous neuromodulation. Epigenetic regulation after PRF is plausible because chronic pain causes transcriptional modifications and electrical neuromodulation may influence chromatin-based gene control.

Objective: To summarize preclinical evidence on epigenetic and molecular changes after PRF applied to the DRG or peripheral nerves.

Methods: PubMed, Embase, and Scopus were searched (PRISMA-S); synthesis followed SWiM. Studies assessed direct epigenetic modifications and/or gene/protein expression changes after PRF at DRG or peripheral nerve targets. Risk of bias was evaluated using the JBI checklist for animal studies.

Results: Seventeen rodent studies were included. One study reported a direct epigenetic modification, showing that PRF reversed complete Freund's adjuvant (CFA)-induced histone H3/H4 hypoacetylation at the *Kcc2* locus, restoring KCC2 expression. Other studies linked PRF to attenuation of microglial/MAPK signaling, modulation of neurotrophic mediators, downregulation of pro-inflammatory cytokines, and normalization of sensory neuron excitability markers across DRG, sciatic nerve, and spinal dorsal horn tissue. Target-specific trends emerged: DRG PRF more consistently attenuated spinal microglial/MAPK signaling, whereas sciatic PRF emphasized normalization of DRG channels/neuropeptides. No human studies and no circulating epigenetic biomarkers were identified.

Conclusion: Preclinical data support a non-destructive PRF mechanism involving dampening of neuro-immune signaling and restoration of inhibitory tone. Direct epigenetic evidence remains limited (single study) and absent in humans. Priorities include standardized PRF parameter reporting, time-course and multi-omic profiling beyond *Kcc2*, and prospective clinical studies incorporating molecular endpoints and circulating epigenetic readouts.

Keywords: pulsed radiofrequency, dorsal root ganglion, neuropathic pain, epigenetics, histone acetylation, microglia, MAPK, KCC2, TRPV1, GDNF

Introduction

The clinical use of radiofrequency (RF) procedures in pain medicine has expanded, particularly for refractory neuropathic and inflammatory conditions.[1–3] Clinical applications of pulsed and conventional RF have also been reported in human pain conditions, including knee osteoarthritis and lumbar facet joint pain.[4–6] PRF, delivered at sub-neurodestructive temperatures, is applied to the dorsal root ganglion (DRG) and peripheral nerves to modulate nociceptive signaling without thermal lesioning. Despite widespread adoption, the mechanisms of action remain only partially understood.

Crucially, the current body of mechanistic evidence is exclusively preclinical in murine models; to our knowledge, no human studies have directly evaluated molecular or epigenetic effects of PRF at DRG or peripheral nerve targets. Across

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rodent experiments, PRF has been associated with changes in gene/protein expression within pain and neuroimmune pathways (*eg*, IRF8, BDNF, P2X3, TRPV1/CGRP, p-ERK/p38/JNK, substance P, GABAB/KCC2) in DRG, nerve, and spinal cord tissues.[7–13]

Only one study has reported directly measured epigenetic modifications following PRF (histone acetylation at the Kcc2 locus),[14] while the remaining literature infers mechanistic plausibility from downstream transcriptional or protein changes. Notably, no studies have measured circulating epigenetic biomarkers (*eg*, plasma/serum miRNAs) before and after PRF.

This systematic review synthesizes the available evidence on PRF at the DRG and peripheral nerves, focusing on directly measured epigenetic changes and molecular alterations (mRNA/proteins) within pain and neuroinflammation pathways. Our aim is to clarify the biological plausibility of PRF while highlighting key gaps—the absence of human data, the scarcity of direct epigenetic measurements, and the complete lack of circulating epigenetic readouts—to guide future translational research.

Methods

Study Design and Research Question

We conducted a systematic review in accordance with the PRISMA 2020 statement. The review protocol was not prospectively registered (eg, PROSPERO). The search strategy was documented following PRISMA-S,[15] and the qualitative synthesis was reported according to SWiM[16] (Figure 1). Our objective was to assess how RF—with a focus on PRF—applied to the DRG/nerve roots or to peripheral nerves (eg, sciatic or medial branches) is associated with epigenetic alterations and/or changes in gene/protein expression relevant to antinociceptive mechanisms. Risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for experimental animal studies, supplemented by domains from the SYRCLE and ARRIVE guidelines.

Information Sources and Search Strategy

We searched PubMed, Embase, and Scopus. Search strings combined RF terms ("pulsed radiofrequency"/"radiofrequency") with epigenetic terms (epigenetic*histone*methyl*miRNA/lncRNA) and molecular terms (gene/protein expression), paired with pain/neuropath*/inflamm* keywords. The full PubMed search strategy is reported in Table 1, together with the complete search strategies for Embase and Scopus.

Eligibility Criteria

We considered eligible preclinical and clinical studies investigating the effects of PRF delivered to the DRG/nerve roots or peripheral nerves on biological outcomes relevant to nociception. The primary outcome was the presence of directly measured epigenetic modifications, including DNA methylation, histone modifications (eg, via ChIP), and non-coding RNAs (miRNA/lncRNA), as well as potential circulating epigenetic biomarkers. In the absence of direct epigenetic measures, we included studies reporting changes in gene or protein expression within key pain- and neuroinflammation-related pathways (eg, IRF8, BDNF, KCC2, P2X3, TRPV1/CGRP, p-ERK/p38/JNK, substance P, GABAB). Reasons for exclusion were: absence of PRF procedure; absence of epigenetic/molecular measures; insufficient data.

Study Selection

Screening proceeded in two stages: first title/abstract review for preliminary eligibility; and then full-text assessment to confirm inclusion and allocate each study to the target (DRG/roots vs peripheral nerve) and outcome type (direct epigenetics vs expression).

Quality Assessment and Risk of Bias

Given the heterogeneity of study designs, we performed a qualitative appraisal across key domains: randomization and blinding, completeness of PRF parameter reporting, sample size, appropriateness of molecular methods (eg, antibody/primer specificity and normalization), use of controls, and reporting transparency. In addition, we applied the JBI Critical

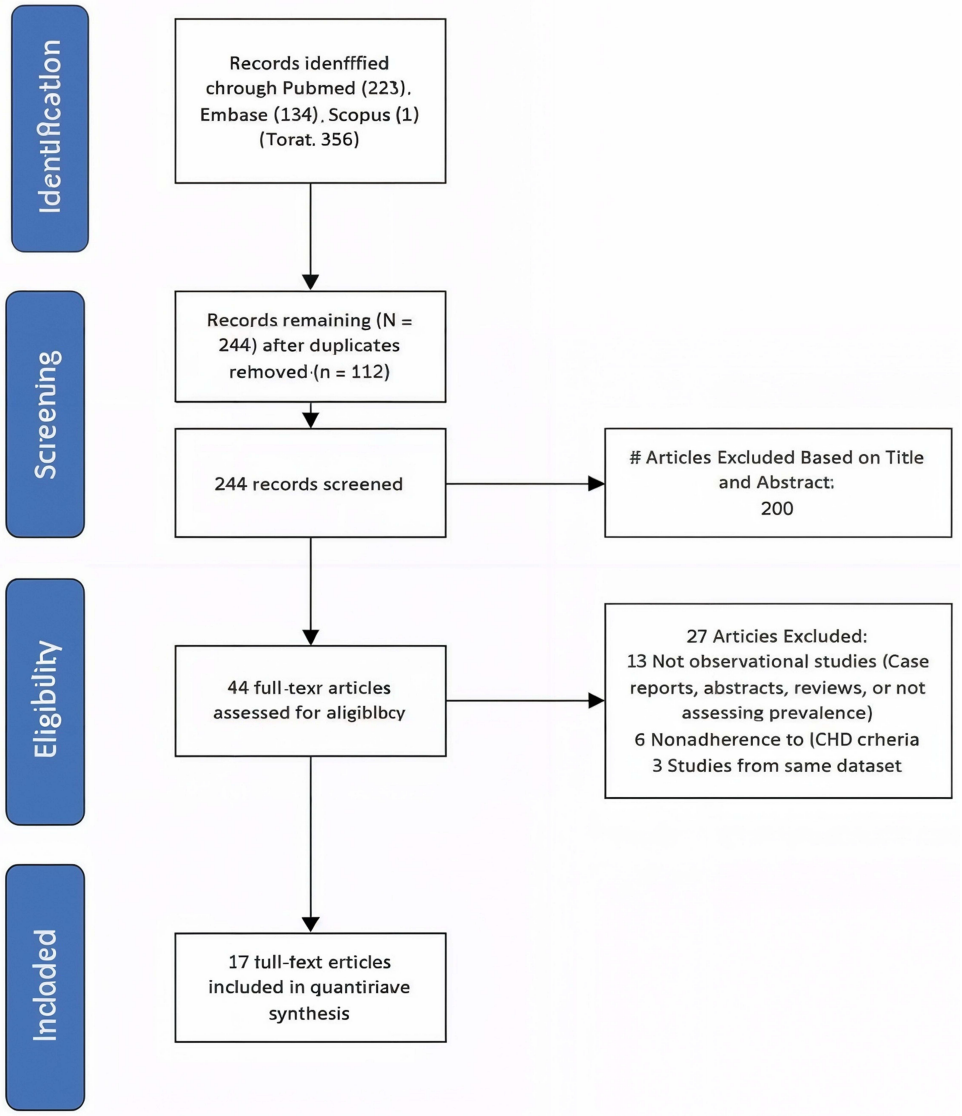

Figure 1 PRISMA-S 2020 flow diagram summarizing the study selection process.

Appraisal Checklist for experimental animal studies, with each study evaluated across 10 domains (yes/no/unclear) and results summarized in Table 2. Most studies showed unclear risk in randomization and blinding, frequent incomplete reporting of PRF parameters, but consistent strengths in outcome validity and statistical analysis. As conceptual references, we also considered the SYRCLE and ARRIVE guidelines[17–19] for animal studies and general risk-of-bias principles for clinical research.

The study selection process is illustrated in Figure 1, following the PRISMA 2020 guidelines. A total of 17 preclinical rodent studies met the eligibility criteria and were included in the final synthesis. The diagram shows the number of records identified through database searching (PubMed, Embase, and Scopus), the number of duplicates removed, records screened, full-text articles assessed for eligibility, and the final 17 preclinical studies included in the systematic review. Reasons for exclusion at the full-text stage are detailed in the diagram.

Study Selection and Characteristics

A total of 17 preclinical rodent studies met the eligibility criteria and were included in the final synthesis. The study selection process is illustrated in Figure 1 (PRISMA 2020 flow diagram). Screening proceeded in two stages: first title/abstract review for preliminary eligibility, followed by full-text assessment to confirm inclusion and allocation of each

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Table 1 The Full PubMed, Embase and Scopus Search Strategies

Database	Fields/Syntax	Search String	Coverage	Notes
PubMed	Title/Abstract fields; quoted phrases; Boolean AND/OR	(("pulsed radiofrequency"[Title/Abstract] OR "PRF"[Title/Abstract] OR "radiofrequency"[Title/Abstract]) AND (epigenetic*[Title/Abstract] OR histone*[Title/Abstract] OR methyl*[Title/Abstract] OR "miRNA"[Title/Abstract] OR "lncRNA"[Title/Abstract]) AND (pain[Title/Abstract] OR neuropath*[Title/Abstract] OR inflamm*[Title/Abstract]))	June 30, 2025	No language/date limits; reference lists screened
Embase	ab,ti fields; Emtree-compatible; Boolean AND/OR	("pulsed radiofrequency":ab,ti OR "PRF":ab,ti OR "radiofrequency":ab,ti) AND (epigenetic*:ab,ti OR histone*:ab,ti OR methyl*:ab,ti OR miRNA:ab,ti OR lncRNA:ab,ti) AND (pain:ab,ti OR neuropath*:ab,ti OR inflamm*:ab,ti)	June 30, 2025	No language/date limits; reference lists screened
Scopus	TITLE-ABS-KEY fields; Boolean AND/OR	TITLE-ABS-KEY("pulsed radiofrequency" OR PRF OR "radiofrequency") AND TITLE-ABS-KEY(epigenetic* OR histone* OR methyl* OR miRNA OR lncRNA) AND TITLE-ABS-KEY(pain OR neuropath* OR inflamm*) Notes - All databases were searched up to June 30, 2025. - No filters for study design or species were applied at the search stage. - Reference lists of relevant reviews and included studies were manually screened to identify additional eligible articles.	June 30, 2025	No language/date limits; reference lists screened

study to the target (dorsal root ganglion/nerve roots vs peripheral nerves) and outcome type (direct epigenetic measures vs molecular expression changes). Reasons for exclusion were recorded and are detailed in the PRISMA diagram.

The included studies involved PRF delivered to either the DRG/nerve roots or the sciatic/peripheral nerves. Molecular readouts comprised gene and protein expression in DRG, sciatic nerve, and spinal dorsal horn; only one study reported direct epigenetic modifications at the *Kcc2* locus. Behavioral outcomes (mechanical and thermal thresholds) accompanied most experiments, while reporting of PRF parameters (eg, voltage, pulse width/interval, exposure time) was variably complete. Risk-of-bias assessment highlighted recurrent limitations, including incomplete reporting of PRF settings, lack of blinding and randomization details, and small sample sizes. Full JBI checklist results for each study are reported in Table 2.

Results

DRG/Nerve-Root Targets

Across DRG-targeted studies, convergent changes appeared in neuro-immune and synaptic pathways. In the spinal cord, PRF was associated with reductions in IRF8, microglial markers (Iba1), and phosphorylated MAPKs (p-p38 and p-ERK), changes that paralleled analgesic effects.[7,8,20] BDNF modulation was also observed in line with pain relief.[8,29] At the DRG level, Nav1.7 was consistently down-regulated, with high-voltage PRF showing stronger effects than standard settings.[21] High-voltage PRF also increased GRK2 and reduced p-p38, consistent with dampened neuroinflammation.[20] In mixed-target models, PRF reduced circulating IL-1β and TNF-α as well as spinal β-catenin, alongside behavioral improvement.[13] Early transcriptomic profiling further demonstrated PRF-induced gene expression changes spanning nerve–DRG–spinal cord.[22]

Table 2 JBI Critical Appraisal Checklist for Animal Studies

Study	Randomization	Allocation Concealment	Animals Similar	Blinding Caregivers	Blinding Assessors	Follow-Up	Outcome Measures	Statistical Analysis	PRF Parameters	COI/ Funding	Total Score
Liu 2018[7]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Xu 2019[8]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Fu 2019[9]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Ren 2018[10]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Chen 2014[11]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Wang 2020[12]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Jiang 2019[13]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Liu 2017[14]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Xu 2024[20]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Dai 2022[21]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Vallejo 2013[22]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Koshida 2023[23]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Hidaka 2022[24]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Lee 2015[25]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Lyu 2023[26]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Unclear	No	5
Jia 2016[27]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6
Jin 2018[28]	Unclear	No	Yes	No	Unclear	Yes	Yes	Yes	Yes	No	6

Notes: Each Included Study Was Evaluated Using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Experimental Animal Studies. Responses are Coded as Yes/No/Unclear. A Total Score Was Calculated for Each Study (Yes = 1, No/Unclear = 0).

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Sciatic Nerve Target

When PRF was applied to the sciatic nerve, molecular alterations were observed across DRG, nerve, and spinal tissue. At the DRG, PRF normalized TRPV1/CGRP expression and modulated BDNF in resiniferatoxin-induced neuropathy.[23] Early post-injury PRF produced greater suppression of p-ERK and Nav1.7 than delayed treatment.[24] Expression of the purinoceptor P2X3 decreased in both DRG and dorsal horn.[9] Neuropeptide and cytokine changes included reduced CGRP in DRG,[10] decreased substance P in the dorsal horn,[12] and down-regulation of TNF-α in sciatic nerve and spinal cord.[25] Sciatic PRF also influenced the pain–depression interplay, reducing spinal IRF8 while increasing prefrontal BDNF, paralleling improvements in pain-induced depressive-like behavior.[26] In inflammatory pain models, PRF attenuated CFA-induced hyperalgesia via spinal JNK modulation.[11] Finally, studies targeting the ligation site demonstrated increased GDNF expression (both mRNA and protein), with associated behavioral improvements and ultrastructural recovery.[27,28]

Direct Epigenetic Readouts

Only one study to date has reported direct epigenetic measurements after PRF exposure. Liu and coworkers[14] demonstrated that PRF attenuated CFA-induced histone H3/H4 hypoacetylation at the *Kcc2* locus, thereby restoring KCC2 expression and inhibitory tone within spinal circuits. This finding provides the first mechanistic link between PRF delivery and epigenetic regulation of neuronal inhibition. Beyond this study, no experimental work has investigated DNA methylation, histone modifications at other loci, or non-coding RNAs in a hypothesis-driven, target-specific manner following PRF. Furthermore, no studies have evaluated circulating epigenetic biomarkers such as plasma or serum miRNAs, DNA methylation signatures, or histone marks, underscoring a critical gap for future translational research.

A schematic synthesis of these molecular and epigenetic changes induced by PRF across DRG, sciatic nerve, and spinal cord is presented in Figure 2.

The diagram illustrates convergent preclinical findings: suppression of microglial/IRF8 and MAPK signaling at the DRG; normalization of TRPV1, CGRP, P2X3, and Substance P at the sciatic nerve; and spinal changes including increased BDNF, GDNF, and KCC2 (epigenetic regulation), together with reductions in pro-inflammatory cytokines (IL-1β, TNF-α) and β-catenin. Arrows indicate the direction of proposed effects.

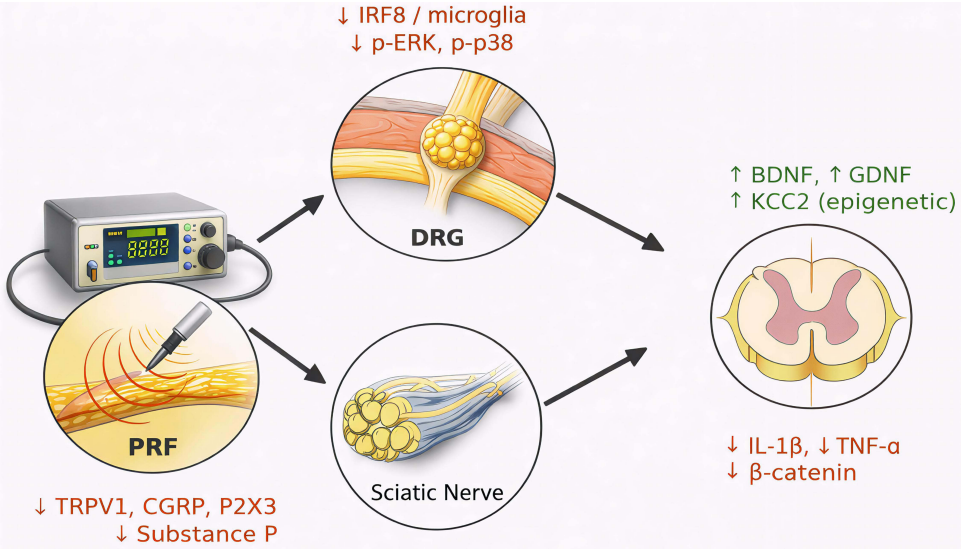

Figure 2 Mechanistic effects of pulsed radiofrequency (PRF) across DRG, sciatic nerve, and spinal cord. The red arrows indicate a decrease in concentration. The green arrows indicate an increase in concentration.

Discussion

This systematic review indicates that PRF applied to the DRG or peripheral nerves in rodent models is associated with gene expression changes across neuro-immune and synaptic pathways in the DRG, sciatic nerve, and spinal dorsal horn. Taken together, the data support a biologically plausible, *non-neurodestructive* mechanism of action in which PRF dampens microglial signaling and excitatory transmission while favoring inhibitory tone. At the same time, the evidence base remains preclinical, heterogeneous in reporting of PRF parameters, and—with one exception—limited to downstream transcriptional/protein readouts rather than direct epigenetic measures.

Multiple DRG-targeted studies converge on attenuation of microglia/IRF8 pathways and MAPK activation in the dorsal horn, paralleling behavioral analgesia. Reduced IRF8, Iba1, and p-p38/p-ERK suggest that PRF counters glial priming and inflammatory amplification within spinal circuits. In a mixed-target model, decreases in circulating IL-1β/TNF-α accompanied reductions in spinal β-catenin, linking peripheral immune tone to central signaling. These findings are mechanistically coherent with earlier tract-wide transcriptomic shifts after PRF across nerve → DRG → spinal cord (Table 3).

Table 3 Molecular/Signaling Factor Names, Targets, Mechanism of Action, Pathways Affected, and Therapeutic Uses

Name	Target (s)	Mechanism of Action	Pathway (s) Affected	Therapeutic Use
Phospho-JNK (p-JNK)	c-Jun, ATF2, Bim, other stress-responsive substrates	Activated SAPK phosphorylating transcription factors to drive AP-1–dependent gene expression and stress responses	MAPK/JNK (stress-activated), AP-1 transcription	JNK inhibition explored for inflammatory and neuropathic pain
KCC2 (SLC12A5)	K^+/Cl^- cotransport	Extrudes Cl^- to maintain low neuronal $[Cl^-]i$, preserving hyperpolarizing GABA_A/glycine currents	Chloride homeostasis; inhibitory neurotransmission	KCC2 enhancers to restore inhibition in epilepsy, spasticity, neuropathic pain (investigational)
Histone H3/H4 acetylation	Histone H3/H4 lysine residues	Acetylation by HATs loosens chromatin, increasing transcription; deacetylation by HDACs represses genes	Epigenetic chromatin remodeling; activity-dependent transcription	HDAC/HAT modulators for pain and neuropsychiatric disorders (context-dependent)
IRF8	ISRE DNA motifs; microglial gene promoters	Transcription factor promoting microglial activation and pro-inflammatory gene programs	TLR/IFN signaling; microglial activation	IRF8 pathway inhibition for neuroinflammation/neuropathic pain (investigational)
Iba1 (AIF1)	F-actin; Ca^{2+} binding	Actin-bundling protein regulating membrane ruffling and phagocytosis in microglia; activation marker	Cytoskeletal dynamics; innate immune responses	Biomarker of microglial activation; not a direct drug target
Phospho-p38 (p-p38 MAPK)	ATF2, MK2/3, HSP27, cytokine regulators	Stress kinase driving inflammatory mediator production and nociceptive sensitization	MAPK/p38; inflammatory gene expression	p38 inhibitors as anti-inflammatory /analgesic candidates
IL-1β	IL-1R1	Pro-inflammatory cytokine activating NF-κB/MAPK, promoting glial activation and neuronal sensitization	NF-κB, MAPK; inflammasome outputs	IL-1 pathway blockade for autoimmune/inflammatory conditions; analgesic benefit in subsets
TNF-α	TNFR1/TNFR2	Cytokine triggering NF-κB/MAPK, up-regulating adhesion molecules and pronociceptive mediators	NF-κB, MAPK; apoptosis/survival signaling	Anti-TNF biologics for immune diseases; variable analgesic effects
β-Catenin	TCF/LEF transcription factors; cadherin–catenin complexes	Nuclear co-activator in Wnt signaling; scaffolds adherens junctions at membrane	Wnt/β-catenin transcription; cell–cell adhesion	Wnt/β-catenin modulators in cancer/fibrosis; pain modulation investigational
BDNF	TrkB (NTRK2)	Neurotrophin activating TrkB→PLCγ/PI3K/ERK; modulates synaptic plasticity; can down-regulate KCC2	Neurotrophic signaling; plasticity; disinhibition	TrkB-targeted therapies for neuroprotection; mixed effects in pain (context-dependent)
PI3K (class I)	Phosphoinositides ($PIP_2 \rightarrow PIP_3$)	Lipid kinase generating PIP_3 to recruit/activate AKT and downstream effectors	PI3K/AKT/mTOR; survival and plasticity	PI3K inhibitors in oncology; analgesic modulation investigational

(*Continued*)

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Table 3 (Continued).

Name	Target (s)	Mechanism of Action	Pathway (s) Affected	Therapeutic Use
Phospho-ERK (p-ERK1/2)	Elk-1, RSK, CREB, ion channel regulators	Canonical MAPK driving activity-dependent transcription and central sensitization	Ras/Raf/MEK/ERK; AP-1/CREB	MEK/ERK inhibitors (oncology); antinociceptive potential under study
Nav1.7 (SCN9A)	Voltage sensor; Na^+ permeation pathway	TTX-sensitive voltage-gated Na^+ channel critical for nociceptor excitability and spike initiation	Peripheral excitability; pain pathway transmission	Selective Nav1.7 blockers for analgesia (investigational)
GRK2 (ADRBK1)	Activated GPCRs; β-arrestin recruitment	Phosphorylates agonist-occupied GPCRs to drive desensitization and biased signaling	GPCR regulation; cAMP/PKA and β-arrestin pathways	GRK2 modulation to enhance analgesic GPCR tone; cardiovascular uses under study
IL-6	IL-6Rα/gp130	Cytokine activating JAK/STAT3 (and MAPK/PI3K) with pleiotropic pro-/anti-inflammatory effects	JAK/STAT3; acute-phase response	IL-6R blockade for autoimmune disease; analgesic benefit in select conditions
GABA_B-R1 (GABAB1)	GABA; partners with GABAB2; GIRK/VGCC via Gβγ	Gi/o-coupled GPCR inhibiting AC, opening GIRK and reducing Ca^{2+} influx → decreased neurotransmitter release	Inhibitory GPCR signaling; presynaptic inhibition	Baclofen (agonist) for spasticity; analgesia in some neuropathic states
Na^+/K^+-ATPase	Na^+, K^+, ATP; cardiotonic steroids (inhibitors)	Electrogenic pump maintaining Na^+/K^+ gradients and membrane potential	Ion homeostasis; excitability; secondary transport	Cardiac glycosides in HF; not an analgesic target
5-HT3 receptor (HTR3)	Serotonin (5-HT)	Ligand-gated cation channel mediating fast excitatory serotonergic transmission	Cys-loop ion channel signaling; emesis circuits; nociception	5-HT3 antagonists as antiemetics; analgesic effects context-dependent
c-Fos (FOS)	AP-1 DNA elements (with Jun)	Immediate-early transcription factor marking neuronal activation and driving AP-1 programs	Activity-dependent transcription; MAPK/ERK-linked	Biomarker of activation; not a validated therapeutic target
GDNF	GFRα1/RET	Neurotrophic factor promoting survival and sensitization via RET tyrosine kinase	RET→MAPK/PI3K signaling; neuronal plasticity	Neurorestorative strategies; effects on pain are context-dependent
CGRP (CALCA)	CGRP receptor (CLR/RAMP1)	Gs-coupled GPCR agonist increasing cAMP; potent vasodilator; pronociceptive	cAMP/PKA; trigeminovascular signaling	CGRP antagonists and mAbs for migraine prevention/acute treatment
P2X3 receptor (P2RX3)	ATP	Homotrimeric ligand-gated cation channel on sensory neurons mediating nociceptor activation	Purinergic signaling; peripheral sensitization	P2X3 antagonists for chronic cough; analgesia under investigation
Substance P (TAC1)	NK1 receptor (TACR1)	Gq-coupled neuropeptide driving PLC/PKC signaling, neurogenic inflammation, and nociceptive transmission	NK1→PLC/IP_3/DAG; central/peripheral sensitization	NK1 antagonists as antiemetics; limited analgesic efficacy to date

At the DRG, high-voltage PRF (HV-PRF) down-regulated Nav1.7 and improved ultrastructure, whereas early-after-injury PRF more effectively suppressed p-ERK and Nav1.7 than delayed application, underscoring a timing/parameter dependence of molecular effects. Along the peptidergic axis, PRF lowered CGRP in the DRG and Substance P in the dorsal horn, while P2X3 purinoceptors were reduced in DRG and dorsal horn. In resiniferatoxin-induced neuropathy, PRF normalized TRPV1/CGRP and modulated BDNF. Two sciatic-nerve studies showed GDNF up-regulation with behavioral improvement and ultrastructural recovery. Together with DRG-targeted work reporting BDNF modulation[30] and the pain–depression link (↓ spinal IRF8, ↑ prefrontal BDNF) after sciatic PRF, these results support a broader neuro-immune–neurotrophic model for PRF.

The most compelling mechanistic clue is restoration of spinal inhibitory tone. The only study with direct epigenetic measurement demonstrated that PRF countered CFA-induced histone (H3/H4) hypoacetylation at the *Kcc2* locus, restoring KCC2 expression. This provides a concrete molecular bridge between PRF delivery and disinhibition reversal.

Spinal met-enkephalin increased after PRF, supporting enhanced inhibitory transmission.[31] Other studies align indirectly: reduced MAPK activation and decreased excitatory mediators (TRPV1/CGRP, Substance P, P2X3) are coherent with a shift toward inhibition. However, beyond Liu 2017, evidence remains indirect; no work has profiled DNA methylation, histone marks beyond H3/H4 at *Kcc2*, or noncoding RNAs in a hypothesis-driven, target-specific fashion after PRF.

DRG-directed PRF repeatedly impacts spinal microglial/MAPK pathways, supporting a principal site of action at primary afferent somata with downstream spinal effects. Sciatic-nerve PRF more often reports DRG peptide/channel normalization (TRPV1/CGRP, P2X3, Nav1.7) and neurotrophin shifts (GDNF, BDNF), yet spinal consequences (eg, ↓ Substance P, ↓ IRF8) still emerge. This pattern supports axon–soma–spinal coupling and suggests that procedural choice (DRG vs peripheral nerve) may be tailored to dominant pain mechanisms, though translational validation is lacking.

The superiority of HV-PRF for Nav1.7 and structural DRG effects, and the enhanced efficacy of earlier PRF after injury,[4] together imply a window of plasticity and a dose–response relationship. Yet reporting of PRF settings (voltage, pulse width/interval, exposure time, tip temperature) is frequently incomplete, hampering cross-study comparison and precluding a formal exposure–response analysis.

Strengths of this work include convergent molecular findings across multiple labs and models (CCI, SNI, resiniferatoxin), consistent behavioral–molecular coupling, and one direct epigenetic demonstration. Limitations are the presence of exclusively rodent data, the heterogeneity of targets, time-points, and PRF parameters, the single time-point sampling in most studies, which obscures temporal trajectories. Sex, strain, and analgesic co-treatments are also variably reported, and blinding/randomization details are inconsistent, increasing risk of bias.

Our JBI risk-of-bias assessment confirmed moderate methodological quality across the included studies (Table 2). Most experiments lacked randomization, allocation concealment, and blinding, while reporting of PRF parameters was incomplete and conflicts of interest were seldom declared. These limitations reduce reproducibility and highlight the need for more rigorous experimental standards in future preclinical work.

The rodent data justify clinical plausibility that PRF may reduce pain by tuning neuro-immune signaling and restoring inhibitory balance without thermal lesioning. However, translation requires human evidence. Indeed, early clinical studies have already demonstrated analgesic benefits of PRF and innovative RF techniques in knee osteoarthritis and lumbar facet joint pain, further reinforcing the translational relevance of these preclinical findings.[5,6,32]

Conclusion

Across murine models, PRF at the DRG or peripheral nerves is consistently associated with molecular shifts spanning microglial/MAPK signaling, ion channels and neuropeptides (eg, P2X3, TRPV1/CGRP, Substance P), and restoration of inhibitory tone (KCC2), in parallel with behavioral analgesia. These findings support a biologically plausible, non-neurodestructive

Future research is needed in order to standardize PRF parameter, to replicate and extend locus-specific epigenetic findings (beyond *Kcc2*) with time-course designs, to incorporate unbiased multi-omic and single-cell approaches across DRG–spinal circuits and to embed mechanistic endpoints in prospective human studies.

Disclosure

The authors report no conflicts of interest in this work.

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