International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	NEUROINFLAMMATION AFTER MUSCULOSKELETAL TRAUMA - MISSING LINK BETWEEN ORTHOPEDIC INJURY AND CHRONIC PAIN?
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5566
RECEIVED	26 February 2026
ACCEPTED	28 May 2026
PUBLISHED	08 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

NEUROINFLAMMATION AFTER MUSCULOSKELETAL TRAUMA - MISSING LINK BETWEEN ORTHOPEDIC INJURY AND CHRONIC PAIN?

Agnieszka Morawa *(Corresponding Author, Email: agnieszkamorawa@gmail.com)*
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0001-2325-7998

Sonia Mojzyk
7th Navy Hospital, Gdańsk, Poland
ORCID ID: 0009-0008-6397-7739

Judyta Bordakiewicz
7th Navy Hospital, Gdańsk, Poland
ORCID ID: 0009-0001-7286-0662

Zuzanna Michalska
Clinical Hospital of the Ministry of Internal Affairs and Administration with the Warmia-Mazury Oncology Centre, Olsztyn, Poland
ORCID ID: 0009-0005-8775-102X

Donata Pokorska
The Voivodal Specialistic Hospital, Olsztyn, Poland
ORCID ID: 0009-0005-6271-3465

Julia Świechowska
Uniwersyteckie Centrum Kliniczne w Gdańsku, Gdańsk, Poland
ORCID ID: 0000-0001-6492-6863

Zuzanna Zarzycka
7th Navy Hospital, Gdańsk, Poland
ORCID ID: 0009-0008-1374-5876

Julia Maria Kuczkowska
7th Navy Hospital, Gdańsk, Poland
ORCID ID: 0009-0004-8320-876X

Ingrid Samberger
7th Navy Hospital, Gdańsk, Poland
ORCID ID: 0009-0002-6906-6852

Magdalena Wiciak
Uniwersyteckie Centrum Kliniczne w Gdańsku, Gdańsk, Poland
ORCID ID: 0009-0007-9221-4063

ABSTRACT

Musculoskeletal injuries, such as fractures and whiplash, affect around 9 million people annually and are a major cause of disability. In many cases, pain persists despite tissue healing, which is not fully explained by traditional models. Increasing evidence suggests that neuroinflammation - the activation of the innate immune system in the peripheral and central nervous systems - may underlie chronic pain. It involves glial cell activation and the release of proinflammatory mediators, leading to central sensitization and maladaptive synaptic plasticity. To evaluate neuroinflammation as a potential "missing link" between orthopedic injury and chronic pain, and to identify therapeutic targets. A search of PubMed, Web of Science and Google Scholar was conducted. Included were randomized controlled trials, systematic review and meta-analyses of ankle sprain treatment and rehabilitation strategies.

Neuroinflammation contributes to the transition from acute to chronic pain beyond tissue healing. Glial activation and mediators, such as TNF-α and IL-1β, drive central sensitization, while caspase cascades (caspase-1, -3, -6) regulate AMPA and NMDA receptor trafficking in the spinal cord, maintaining hypersensitivity. Clinical findings, including MRI studies of whiplash patients, demonstrate nerve root inflammation associated with hyperalgesia. Emerging therapies, such as transcutaneous vagus nerve stimulation (tVNS) and exosome-based approaches, show promise in modulating these processes.

Neuroinflammation links musculoskeletal injury to persistent pain by combining immune activation and neural changes that sustain central sensitization. Understanding these mechanisms may help identify patients at risk and guide the development of treatments targeting neuroinflammation to prevent chronic pain.

KEYWORDS

Neuroinflammation, Musculoskeletal Trauma, Neuroinflammatory Signaling, Central Sensitization, Chronic Fracture Pain

CITATION

Agnieszka Morawa, Sonia Mojzyk, Judyta Bordakiewicz, Zuzanna Michalska, Donata Pokorska, Julia Świechowska, Zuzanna Zarzycka, Julia Maria Kuczkowska, Ingrid Samberger, Magdalena Wiciak. (2026) Neuroinflammation After Musculoskeletal Trauma - Missing Link Between Orthopedic Injury and Chronic Pain? *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5566

1. Introduction

Musculoskeletal injuries, resulting from physical trauma or osteoporosis, are a leading cause of morbidity, disability and mortality worldwide [1]. The estimated incidence of fractures in the population ranges from 2 to 5 per 100 person-years. In Europe alone, their number is predicted to increase by 23% over the next decade due to population aging [2, 3].

The scale of the problem is enormous - approximately 9 million osteoporotic fractures occur worldwide annually, and in China alone, the number of traumatic fractures exceeds 4.4 million annually [1]. Other conditions, such as osteoarthritis, affect over 240 million people globally, while cartilage abnormalities are found in 61-63% of patients undergoing arthroscopy [4, 5].

The social and economic costs of these injuries are colossal and place a huge burden on healthcare systems. In the UK, whiplash injuries alone cost around £3 billion annually, primarily due to medical expenses [6, 7]. In the United States, the total economic cost of chronic pain reaches $635 billion annually, and osteoarthritis-related costs in developed countries account for between 1% and 2.5% of GDP [8, 4]. Hip fractures generate the highest individual costs (over $30,000) with devastating social consequences - nearly one in three patients over the age of 50 dies within a year of a hip fracture [3].

Typical sequelae include both immediate tissue damage and long-term functional complications: mechanical allodynia or nonunion after fractures [1, 2], nerve damage, joint cartilage damage leading to swelling, pain and accelerated degenerative changes [5]. Many fractures require orthopedic surgery, which are invasive procedures, although necessary for stabilization, can induce neuroinflammation, which is crucial for the progression of acute pain to pathological chronic pain [1]. Postoperative complications also include

infections (osteomyelitis), which occur in 1-2% of closed fractures and up to 30% of open fractures, and can even lead to amputation [3]. These injuries and their sequelae not only impair physical function but are also strongly correlated with poor mental health, causing depression, anxiety and post-traumatic stress disorder (PTSD) [1, 4, 9].

Chronic pain is defined as pain that persists or recurs for more than 3 months, exceeding the typical time required for tissue healing [1]. It is considered the "fifth vital sign" and its characteristics include spontaneous pain, allodynia and hyperalgesia [10]. The rate of transition from acute to chronic pain after musculoskeletal injuries is highly variable, ranging from 11% to 56% [11]. For specific injuries, these rates are particularly high: chronic pain affects 61,7% of patients after ankle and knee fractures, and 55,1% after tibia fractures [1]. In patients with whiplash injuries (WADII), approximately 50% of individuals struggle with chronic symptoms lasting more than 5 years [7]. The classic biomechanical model has significant shortcomings in explaining the pathogenesis of pain, as studies indicate a poor correlation between radiographic damage and pain intensity [4]. Traditional diagnostic criteria (e.g., for WADII) rely solely on routine clinical tests, which often fail to detect subtle neural pathologies despite the presence of neuropathic symptoms in patients, such as a reduced vibration threshold or somatosensory hyperalgesia [6, 7]. In nociplastic pain, symptoms occur even in the absence of clear evidence of tissue or somatosensory damage [12]. The transition from acute to chronic pain remains elusive. Currently, the molecular mechanisms responsible for the transformation of physiological post-traumatic pain into pathological pain remain poorly understood, which constitutes a major obstacle to the development of effective targeted drugs [1, 11]. This gap stems, among other things, from the difficulty of conducting long-term, invasive studies in humans and the significant heterogeneity of immune and pain responses across patients [11].

A growing body of evidence suggests that a key "missing link" in pain physiology is neuroinflammation, or the activation of the innate immune system within the nervous system [13]. Neuron-glia interactions, in which microglia and astrocytes release mediators (e.g., cytokines IL-1β, IL-6, TNF-α and caspases) are attracting particular attention among researchers. This leads to pathological synaptic plasticity and central sensitization [1, 13]. Understanding these mechanisms, including the role of caspase cascades (caspase-1, -3 and -6) in regulating AMPA and NMDA receptor trafficking, opens new avenues for therapies to prevent chronic pain following orthopedic surgery and fractures [1, 10].

The main aim of this paper is to review current knowledge on the role of inflammatory processes within the nervous system following musculoskeletal injuries. The paper focuses on assessing whether neuroinflammation constitutes a "missing link" in the pathophysiological transition from acute post-traumatic pain to persistent chronic pain, which often persists despite anatomical healing of peripheral tissues [7].

To achieve this aim, the paper aims to:

- analyze the molecular and cellular mechanisms of neuron-glia interactions, with particular emphasis and the role of caspase cascades in the spinal cord,
- examine how inflammatory signals generated at the site of orthopedic injury (e.g., fracture or whiplash) are transformed into maladaptive synaptic plasticity and central sensitization.
- assessing the usefulness of modern diagnostic methods, such as magnetic resonance imaging (MRI), in identifying objective markers of neuroinflammation in patients
- identifying potential therapeutic targets that can prevent pain chronification by suppressing inflammation in the nervous system.

Understanding neuroinflammation as a key element of pathogenesis will allow for the redefinition of orthopedic pain from a symptom of tissue damage to a complex disease of the neuroimmune system.

2. Methodology

This narrative review synthesizes recent searches about neuroinflammatory after orthopedic injuries and their impact on chronic pain. Searches for source articles were conducted through sites such as PubMed, Google Scholar and Scopus, most of them date back up to 15 years, individual sources may be older. Key terms search included: neuroinflammation, chronic pain, musculoskeletal trauma, soft tissue injury, neuroinflammatory signaling, microglia, synaptic plasticity, central sensitization, pro-inflammatory cytokines, chronic fracture pain, nociplastic pain, exosomes and neuromodulation. This article includes studies, originally peer-reviewed and published in English, focused on the impact of orthopedic injuries and associated neuroinflammation on people's quality of life and the occurrence of chronic pain syndrome. Incomplete text publications and data from non-primary sources were not taken into account. A total of 80 relevant articles were selected and studied. Articles were thematically categorized into seven domains: inflammatory response

after musculoskeletal injury, definition and mechanisms of neuroinflammation, mechanisms of neuroinflammation activation after peripheral injury, experimental evidences, clinical evidence in humans, factors modulating the neuroinflammation development and potential therapeutic goals. This framework guided both the selection and synthesis of results. As a narrative review, this study does not include a formal quality assessment or meta-analysis. However, heterogeneity and methodological validity were considered when interpreting the results.

3. AI

AI tools were employed exclusively for linguistic refinement and to improve processing efficiency, under strict human supervision; all analytical decisions, interpretations, and conclusions were made by human experts.

3.1 Inflammatory Response After Musculoskeletal Injury

3.1.1 Phases of Tissue Healing

Musculoskeletal tissue healing is a multiphase and dynamic process. In bone fractures, four main, overlapping stages are distinguished: hematoma formation, cartilage (soft) callus development, bony (hard) callus development and remodeling [14].

Inflammatory phase and hematoma formation begins immediately after injury due to disruption of blood vessels and the bone matrix [2, 14]. A fracture hematoma forms and clots, forming a temporary scaffold made of a fibrin network [2, 3]. This network serves as a matrix for the influx of inflammatory cells and progenitor cells from the periosteum and bone marrow [2], which release key proinflammatory mediators that stimulate angiogenesis and attract mesenchymal stem cells (MSCs) [2, 3]. Macrophages remove necrotic tissue and fibrin debris through phagocytosis [2]. This phase typically lasts about 5 days [3].

The next phase is soft callus formation. The fibrin network is replaced by granulation tissue [2]. Under hypoxic conditions within the fracture gap, recruited MSCs differentiate into chondrocytes, which produce collagen-rich fibrocartilaginous tissue, forming what is known as soft callus [3, 14]. The soft callus wraps the ends of the fractured bones, providing initial mechanical stabilization [2]. This stage begins approximately 5 days after the injury and lasts about a week [3].

The soft cartilage undergoes ossification through endochondral ossification [3, 14]. Chondrocytes become hypertrophic and undergo apoptosis, and are replaced by osteoblasts, which deposit woven bone [14]. Invasion of blood vessels is essential here to supply oxygen and nutrients required for callus mineralization [2]. This phase lasts up to 4 weeks after the injury [3].

The remodeling stage is the final and longest phase, which can last from several months to many years [3]. The original coarse-fiber bone is gradually replaced by mature lamellar bone [2, 14]. This process is controlled by the balance between osteoclast activity (bone resorption) and osteoblast activity (new matrix formation), regulated by, among others, the RANKL/OPG pathway [2]. Remodeling restores bone to its original shape and mechanical strength, and restores the Haversian canal system, allowing for full functional recovery [2, 3].

In the case of peripheral nerve injury (e.g., the sciatic nerve), healing progresses through phases of early immune activation, extracellular matrix remodeling, and Schwann cell-driven remyelination [15].

In the context of skeletal muscle injuries, this process is described as a sequence of five phases: degeneration and necrosis, inflammation, regeneration, maturation/remodeling, and final functional recovery [16]. Closer coordination of these processes is crucial for successful healing, as disruption can lead to delayed union or the development of pseudoarthrosis [14, 17].

3.1.2 Local Inflammatory Response

The inflammatory response is initiated immediately after injury as a result of damage to the vessels and extracellular matrix [14, 17]. The disruption of cellular barriers leads to the release of endogenous signaling molecular patterns (DAMPs), such as HMGB1, S100 proteins, and ATP. These are recognized by the innate immune system (e.g., tissue macrophages and mast cells) via Toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE) [16]. This process triggers complement activation, which recruits neutrophils and monocytes from circulation to the site of injury, creating a fracture hematoma that serves as a scaffold for further regeneration [14, 16].

3.1.3 Proinflammatory Cytokines (IL-1β, IL-6, TNF-α)

Cytokines are a key regulatory element in the early phase of healing, and their expression typically peaks within the first 24 hours after injury [2].

TNF-α (Tumor Necrosis Factor-α) is released primarily by M1 macrophages and neutrophils, it interacts with TNFR1 receptors on nociceptors, which increases the activity of TRPV1 and Nav1.8 channels, leading to a lower pain threshold (peripheral sensitization) [14, 18].

IL-1β (Interleukin-1β) is produced by activated macrophages, after proteolytic cleavage by caspase-1, it directly increases the excitability of sensory neurons by activating the p38 MAPK pathway [10, 18].

IL-6 participates in promoting nociceptor plasticity and supports central sensitization processes in the spinal cord [1, 4]. Its serum levels strongly correlate with pain intensity in patients [1, 11].

3.1.4 Immune-Nervous System Communication

Neuroimmune crosstalk plays a fundamental role in the transformation of acute pain into chronic pain [18, 19]. Activated nociceptors at the site of injury secrete neuropeptides such as substance P and CGRP, which act as a chemoattractants for macrophages, increasing local inflammation [18]. Simultaneously, cytokines released peripherally and mediators derived from glial cells (microglia and astrocytes) in the spinal cord modify synaptic transmission, leading to central sensitization [18, 20]. If the inflammatory phase is not resolved (failure to transition M1 to M2 macrophages), a self-perpetuating feedback loop develops, in which chronic pain and ongoing immune dysfunction mutually reinforce each other [2, 21].

3.2 Neuroinflammation - Definition and Mechanisms

3.2.1 Definition of Neuroinflammation

Neuroinflammation is defined as the recruitment and activation of the innate immune system of the nervous system (both peripheral and central) in response to tissue injury, disease processes, or medical interventions [13, 22]. Unlike acute pain, which serves a protective function, persistent neuroinflammation is a pathological and maladaptive process leading to changes in plasticity in pain circuits and the development of chronic pain [10, 18]. It constitutes a crucial “missing link” connecting the initial orthopedic injury with long-term central sensitization, which persists even after tissue healing [13].

3.2.2 The Role of Microglia, Astrocytes and Immune Cells

Microglia are the resident immune cells of the central nervous system (CNS), constituting 10-15% of all glial cells. At rest, they monitor synapses and maintain homeostasis. However, following nerve or tissue injury, they undergo rapid proliferation (microgliosis) and a change in morphology to an amoeboid form, allowing them to release mediators that amplify pain signals [13, 23].

Astrocytes are usually activated after microglia (astrogliosis) and play a fundamental role in maintaining chronic inflammation and the late phases of neuropathic pain [4, 13]. By expressing receptors for glutamate, norepinephrine, and purines, astrocytes actively participate in modifying synaptic transmission and enhancing the excitability of neurons in the dorsal horn of the spinal cord [13, 18].

Immune (Infiltrating) cells include, for example, neutrophils, macrophages or lymphocytes. Peripheral macrophages are recruited to the site of injury by neuropeptides (e.g., substance P) and increase the sensitivity of nociceptors [18]. Neutrophils arrive first (within hours), releasing proteases and reactive oxygen species (ROS), which can secondarily damage healthy tissues, while T and B lymphocytes infiltrate the nervous system in the chronic phase, modulating the immune response and enhancing sensitization [2, 16, 18].

3.2.3 Proinflammatory mediators - Cytokines, Chemokines and Prostaglandins

Proinflammatory key cytokine molecules, such as TNF-α, IL-1β and IL-6, directly interact with nociceptor receptors, lowering their activation threshold and enhancing pain transmission [2, 18]. IL-1β plays a particular role, its maturation being controlled by caspase-1 within the NLRP3 inflammasome [10].

Chemokines, such as CCL2 (MCP-1), CCL21 and CX3CL1 (fractalkine) act as potent attractants for immune cells and regulate the critical dialogue between neurons and glia [1, 13, 24]. For example, CCL21 released from damaged neurons activates microglia via the CXCR3 receptor, driving an inflammatory cascade in the spinal cord [1][10].

The main prostaglandin, PGE2, produced by the COX-2 enzyme, interact with receptors on nerve endings, enhancing the generation of action potentials and directly contributing to thermal and mechanical hyperalgesia [8, 25, 18].

3.2.4 Caspases

Caspases (enzymes from the cysteine protease family) play a fundamental and - as recent research indicates - unconventional role in the pathophysiology of chronic pain following injury [10]. Although traditionally associated primarily with programmed cell death (apoptosis), in the nervous system they act as key regulators of neuroinflammation and synaptic plasticity [1, 10].

Human caspases are divided into three main groups:

I. Inflammatory caspases (1, 4, 5, 11, 12) do not participate in apoptosis, but in inflammatory processes and pyroptosis.

II. Apoptosis effector caspases (3, 6, 7) perform massive proteolysis leading to cell death.

III. Apoptosis indicator caspases (2, 8, 9, 10) trigger a signal to initiate apoptosis.

Caspase-1 (inflammatory caspase) is a prototypical member of the inflammatory group and a key component of the NLRP3 inflammasome. When activated by painful stimuli or injury (e.g., sciatic nerve injury), caspase-1 converts inactive pro-cytokines into their mature forms: IL-1β and IL-18. Released cytokines increase nociceptor excitability, facilitating the transmission of pain information to the brain. Inhibition of caspase-1 alleviates mechanical allodynia and thermal hyperalgesia in models of neuropathy [10].

Caspase-3 (effector caspase), although known as an "executor of apoptosis", in chronic pain plays a role as a regulator of synaptic structures [1, 10]. Active caspase-3 is present in postsynaptic structures, where it regulates the remodeling of dendritic spines [1]. Increased caspase-3 activity in the dorsal horn of the spinal cord has been demonstrated in tibial fracture models. It interacts with the LRRTM1 protein to promote the transport of AMPA receptors to synapses, leading to sustained central sensitization and chronic pain [10].

Caspase-6 (effector caspase) is considered a key link in the dialogue between neurons and microglia. Specifically distributed in the axon terminals of C fibers in the spinal cord, where it co-exists with the neuropeptide CGRP. After injury, caspase-6 is released from nerve endings into the extracellular space, where it activates microglia, inducing the secretion of TNF-α [1, 10]. Inhibiting caspase-6 (e.g., with the inhibitor Z-VEID-FMK) effectively reduces postoperative pain and fracture pain by blocking glutamatergic receptor (AMPA) transport and altering dendritic spine density [10].

Highly selective inhibitors are being developed (e.g., Z-YVAD-FMK for caspase-1, Z-DEVD-FMK for caspase-3), which effectively suppress pathological pain in animal models.

In summary, caspases 1, 3, and 6 are critical checkpoints that determine whether pain following orthopedic injury resolves or develops into a chronic disease state through changes in neuroinflammation and synaptic structure [1, 10].

3.3 Mechanisms of Neuroinflammation Activation After Peripheral Injury

3.3.1 Signals From Damaged Tissues

Signals emanating from damaged musculoskeletal tissues constitute a biochemical cascade that not only initiates the healing process but can also lead to pathological sensitization of the nervous system [1, 16].

Immediately after mechanical injury, cellular barriers are disrupted, causing the leakage of signaling molecules called DAMPs (Damage-Associated Molecular Patterns) or alarmins [16]. Under normal conditions, they are hidden inside cells, but once released, they become potent inducers of sterile inflammation [10][16]. DAMPs include HMGB1 (High-mobility group box 1), S100 proteins, ATP and mitochondrial DNA (mtDNA) [16].

DAMPs are detected by pattern recognition receptors (PRRs) present on nociceptive and immune cells (macrophages, mast cells), such as Toll-like receptors (TLR4, TLR2) and the RAGE receptor [4, 16].

At the site of injury, bidirectional communication occurs between nerve endings and immune cells [18]. Activated nociceptors themselves secrete substance P and CGRP, which act as chemoattractants, attracting macrophages and mast cells to the site of injury, thereby intensifying neurogenic inflammation [16, 18]. M1 macrophages secrete these molecules, which directly affect nociceptors, lowering their activation threshold. For example, TNF-α increases the activity of ion channels (e.g., TRPV1 and Nav1.8), which drastically increases the sensitivity of nociceptors [18].

Degradation of cartilage or bone tissue generates additional inflammatory signals. Proteoglycan fragments act as secondary DAMPs, amplifying the local immune response and damaging remaining healthy tissues [1]. Factors stored within the damaged bone matrix, such as TGF-β, FGF-2 or IGF-1, are released. These factors modulate chondrocyte metabolism and may influence synaptic remodeling in the dorsal horn of the spinal cord [3, 5].

Contact of tissue fluids with intracellular components (e.g., cytoskeletal filaments) activats the component system (C3a, C5a molecules). This causes neutrophil recruitment and can lead to the formation of the membrane attack complex (MAC), which further disrupts cell integrity by releasing even more DAMP signals [16].

3.3.2 Peripheral sensitization

Peripheral sensitization is a process of increased excitability and a lowered activation threshold of peripheral nociceptors, which leads to an amplification of pain signals transmitted to the central nervous system [18, 22]. It is a key mechanism responsible for the transformation of acute pain into persistent chronic pain following orthopedic injuries and tissue damage [11, 22].

The main driver of peripheral sensitization is nerve growth factor (NGF), released at the site of injury [11, 22]. NGF binds to TrkA receptors on nociceptor terminals, inducing their hypersensitivity [22]. This process is supported by proinflammatory cytokines such as TNF-α, IL-1β and IL-6, released by macrophages infiltrating the injury site [1, 18].

Inflammatory mediators lower nociceptor activation thresholds through posttranslational modifications of ion channels such as TRPV1 (capsaicin receptor) and TRPA1 [22]. The cytokine TNF-α enhances the activity of sodium channels, particularly Nav1.8, which facilitates the generation of action potentials in response to stimuli [18].

Long-term peripheral sensitization depends on changes in gene expression. NGF has been shown to recruit the Sp4 transcription factor, which promotes the overproduction of TRPV1 and TRPA1 receptors in dorsal root ganglia (DRG) neurons. This allows hypersensitivity to thermal and mechanical stimuli to persist even after the initial injury has healed [22].

Stimulated nociceptors secrete neuropeptides such as substance P and CGRP, which attract macrophages and mast cells, intensifying local inflammation (so-called neurogenic inflammation) [18, 26]. Macrophages in the DRG further increase neuronal excitability by releasing prostaglandins (e.g., PGE2) and nitric oxide [18].

In chronic pain states, pathological nerve fiber ingrowth (sprouting) occurs into tissues that are normally not innervated, as observed, for example, in damaged tendons or intervertebral discs [11, 26]. Peripheral sensitization manifests primarily as allodynia (pain sensation to normally non-painful stimuli, e.g., light touch) and hyperalgesia (excessive pain sensation to painful stimuli) [18, 27, 1].

Understanding these mechanisms allows the development of new targeted therapies, such as caspase inhibitors or NGF-blocking antibodies, which aim to suppress peripheral neuroinflammation and prevent pain chronification [1, 10, 22].

3.3.3 Central sensitization

Central sensitization is defined as the process of enhanced neuronal signaling within the central nervous system (CNS), resulting in pathological pain hypersensitivity. It involves increased reactivity of nociceptive neurons to impulses that are normally subthreshold or painless [12].

In the spinal cord, structural reorganization of synapses and enhancement of spinal reflexes occur, leading to the expansion of pain areas beyond the site of the initial injury (secondary hyperalgesia) [12]. The constant influx of C-fiber signals to the dorsal horn of the spinal cord after orthopedic injury dramatically increases the excitability of second-order neurons, which underlies persistent pain [4].

A key mechanism driving these changes is the activation of microglia, specialized immune cells of the CNS responsible for innate immunity [13]. In response to nerve or peripheral tissue injury, resting microglia rapidly change morphology to an amoeboid form and undergo intense proliferation, a process known as microgliosis. An important signal initiating this process is CSF-1, which is induced in the dorsal root ganglia (DRG) after injury and transported to the spinal cord, where it activates CSF1R receptors on the glial surface [13,18]. In addition, caspase-6 released from the axon terminals of nociceptive fibers in the spinal cord directly stimulates microglia to produce proinflammatory cytokines such as TNF-α [1][10].

Activated microglia release a cascade of mediators, including BDNF, IL-1β, IL-6 and prostaglandins (PGE2), which dramatically increase the intensity of pain signals [10, 13, 20]. These substances modify synaptic transmission by enhancing the activity of glutamate receptors (NMDA and AMPA) and promoting their transport to the postsynaptic membrane [1, 10].

At the same time, disinhibition occurs, i.e., a weakening of inhibitory signals mediated by GABA and glycine, resulting in the uncontrolled flow of nociceptive impulses to the brain [18, 20, 28].

A psychophysical marker of this condition in humans is enhanced temporal summation of pain (TSP), reflecting the wind-up phenomenon, which is particularly severe in patients with neuropathic pain following spinal cord injury [29, 30].

3.4 Experimental evidence

3.4.1 Animal models of orthopaedic injuries

Animal models of fractures, such as the rodent tibial fracture model (TFM), enable analysis of the mechanisms underlying post-traumatic pain, encompassing both local inflammation and changes in the nervous system. In particular, microglial activation and the release of pro-inflammatory cytokines are observed. Although these models do not fully reflect chronic pain in humans, they constitute a valuable tool for studying neuroinflammatory processes and evaluating potential therapies [31]. Studies indicate significant sex differences in the mechanisms of nociceptive hypersensitivity in mice. In males, microglial inflammatory pathways predominate, whereas in females, adaptive immune mechanisms initially prevail, resulting in different responses to treatment [32]. In a rat model, Tian-Zhi Guo and colleagues demonstrated that four weeks of hindlimb immobilisation leads to increased levels of substance P and CGRP, keratinocyte proliferation, c-Fos activation in the spinal cord, and the expression of inflammatory mediators. These changes result in allodynia, oedema, and increased local temperature, resembling the symptoms of CRPS (complex regional pain syndrome). NK1 receptor blockade alleviates these symptoms, and early fracture stabilisation limits the development of hypersensitivity [33]. Koji Wakatsuki and colleagues demonstrated that, in a repeated cold stress (RCS) model in mice, chronic pain is associated with hyperactivation of proprioceptors in the lumbar dorsal root ganglia (DRG) and local activation of microglia along the reflex arc. Microglial ablation significantly reduced pain symptoms [34].

Models of muscle injury and chronic compressive neuropathies enable the study of changes in nerve structure, Schwann cell activity, and inflammatory responses in damaged tissues. Mechanical compression causes ischaemia, inflammation, and macrophage infiltration, leading to increased expression of pro-inflammatory cytokines, including IL-1β, and modulation of TRPA1/TRPV1 channels, thereby sensitising nociceptors [35,36].

Studies of muscle fatigue have shown that even without direct tissue damage, sensitivity to mechanical stimuli may increase, suggesting a role for central modulation of nociception [37].

Microglia activation plays a key role in the maintenance of chronic pain and inflammation. Activation of the PPARγ receptor inhibits the pro-inflammatory M1 phenotype, reduces cytokine expression and alleviates neuropathic pain [39]. The HMGB1 (High Mobility Group Box 1) protein, released by neurons and microglia, exacerbates inflammation by activating RAGE and TLR-4 receptors [40]. Furthermore, the IKKβ enzyme in the NF-κB pathway regulates the inflammatory response in both the central and peripheral nervous systems following spinal cord injury [41]. The P2X7 receptor on microglia mediates neuroinflammation via the NLRP3 inflammasome [42], and blockade of the C/EBPβ–Fcgr1 axis reduces microglial pyroptosis and promotes neurological regeneration [44]. Activation of microglia increases the excitability of dorsal horn neurons and lowers nociceptive thresholds, and its modulation, e.g. with minocycline, may alleviate chronic central pain [43].

Animal models clearly demonstrate that injury induces local and central inflammation, activates microglia and leads to nociceptive hypersensitivity, thereby laying the groundwork for chronic pain.

3.4.2 Neurobiological studies

In patients with radicular pain, increased immune activity is observed in the spinal cord and intervertebral foramina, as confirmed by elevated levels of TSPO – a marker of immune cell activation [45]. The FLRT3 protein (Fibronectin leucine-rich transmembrane protein 3), produced by damaged DRG (dorsal root ganglion) neurons, increases the excitability of the dorsal horn of the spinal cord and induces mechanical allodynia. Blockade of FLRT3 reduces hypersensitivity, highlighting its role in the pathophysiology of neuropathic pain [46]. Peripheral inflammation modifies the transport of AMPAR subunits in the dorsal horn of the spinal cord, contributing to central sensitisation and chronic hypersensitivity [47].

Chronic pain is associated with neuroplastic changes in the structure and function of the brain, including the prefrontal cortex, anterior cingulate cortex, and dorsomedial thalamus, leading to disrupted connectivity within cortical networks and alterations in cognitive and emotional processes [48,49]. Changes in the insular cortex contribute to the maintenance of chronic pain and associated perceptual disturbances [50]. Neurochemical studies have shown elevated levels of GABA+ in the posterior cingulate cortex (PCC) in individuals with migraine and chronic low back pain, suggesting a common neurochemical basis for chronic pain regardless of aetiology [51]. Brain imaging reveals activation of the primary and secondary sensory cortex, insular cortex, cingulate cortex, and prefrontal cortex during painful mechanical stimulation, with individual differences in thalamic activation [52].

Magnetic resonance spectroscopy (MRS) in chronic low back pain has revealed reduced concentrations of N-acetylaspartate, glutamate, myo-inositol, choline, and glucose in key brain regions, indicating a role for biochemical changes in the pathophysiology of CLBP and a potential therapeutic target [53]. Neurobiological studies show that chronic post-traumatic pain is associated with changes in the spinal cord and brain, including the activation of immune cells, neuroplastic modifications, and neurochemical changes that contribute to the persistence of pain hypersensitivity.

3.5. Clinical evidence in humans

3.5.1. Inflammatory biomarkers

Clinical evidence suggests that chronic pain is associated with persistent inflammatory processes, which can be objectively assessed by analyzing inflammatory biomarkers. Particular attention has been paid to pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor alpha (TNF-α), whose levels are elevated in both serum and cerebrospinal fluid in patients with chronic pain [54,55].

Clinical studies have shown that in patients with lumbar spinal stenosis, the concentration of IL-6 in cerebrospinal fluid is significantly elevated and positively correlates with the degree of stenosis. However, it shows no significant correlation with pain intensity or functional mobility, suggesting that IL-6 may reflect the extent of nerve damage rather than the subjective perception of pain [56]. Even more direct evidence for the involvement of neuroinflammatory processes comes from studies of cerebrospinal fluid (CSF), which reflects the biochemical environment of the central nervous system. In the cerebrospinal fluid (CSF) of patients with cervical myelopathy and lumbar radiculopathy, significantly elevated concentrations of IL-6 have been observed, indicating the presence of inflammation and potential damage to the spinal cord or nerve roots. In contrast, TNF-α remained below the detection limit, while IL-1β was detected only sporadically. Notably, IL-6 levels did not correlate with the severity of clinical symptoms [57]. Furthermore, it has been demonstrated that cerebrospinal fluid from patients with chronic pain can induce the production of pro-inflammatory cytokines, including IL-6, in glial cells. This finding suggests the presence of active inflammatory mediators capable of sustaining inflammation within the central nervous system [13]. These observations support the hypothesis that neuroinflammation is not merely a secondary phenomenon but an active mechanism involved in the maintenance of pain [58]. In summary, elevated concentrations of pro-inflammatory cytokines in both blood serum and cerebrospinal fluid provide strong clinical evidence for the involvement of inflammatory processes in the pathogenesis of chronic pain. These findings indicate that persistent activation of the immune system within the central nervous system plays a key role in the transition from acute to chronic pain.

3.5.2. Neuroimaging

Neuroimaging can reveal persistent activation of the nervous system in patients with musculoskeletal pain. Positron emission tomography (PET) studies using TSPO (18 kDa translocator protein) ligands have demonstrated microglial activation in both the spinal cord and brain, correlating with pain intensity [59,60]. Functional magnetic resonance imaging (fMRI) studies have shown altered activity and connectivity in brain regions involved in pain processing in individuals with chronic pain. These alterations are more pronounced in patients with longer pain duration, suggesting that chronic pain may progressively remodel neural networks [61,62].

3.5.3. Correlation with Chronic Pain

Clinical studies indicate that patients undergoing surgery often develop chronic postoperative pain (CPP), which may persist for weeks or months. Despite standard analgesic treatment, many patients continue to report moderate to severe pain [63,64]. Evidence suggests that central sensitization, arising from interactions between the nervous and immune systems, is a key factor in the development and maintenance of CPP. Activation of glial cells, including microglia and astrocytes, promotes the production of pro-inflammatory cytokines, thereby contributing to pain hypersensitivity [65].

3.6. Factors Modulating the Development of Neuroinflammation

The development of neuroinflammation is influenced by several factors that modulate the body's response to injury and pain. Age is a key determinant, with older patients often exhibiting a more pronounced inflammatory response and a higher risk of developing chronic pain following injury [66]. Gender also plays a role, as women may display stronger inflammatory responses and a greater susceptibility to chronic pain after bone injuries [33]. Genetic factors, such as polymorphisms in genes regulating the immune system, can affect individual susceptibility to neuroinflammation [39]. Psychological factors, including stress and pain catastrophizing, may exacerbate inflammatory responses, thereby facilitating the transition from acute to chronic pain [67,68]. Finally, the severity of the injury, including its location and the extent of tissue damage, is critical for the initiation and persistence of neuroinflammation [69].

3.7. Potential therapeutic targets

The experimental and clinical evidence presented in the previous chapters indicates that orthopaedic injuries lead to the activation of microglia, increased levels of pro-inflammatory cytokines, and changes in the spinal cord and brain. These processes result in increased pain transmission and central sensitisation. This knowledge allows for the identification of potential therapeutic strategies that may reduce the risk of acute pain becoming chronic.

Microglial inhibitors, including minocycline, have been studied in patients with chronic pain. Preclinical studies suggest that they may reduce microglial activation and alleviate pain; however, the results of clinical trials remain inconclusive. One randomised trial in patients with chronic low back pain showed no significant improvement, whereas literature reviews suggest potential benefits in selected forms of neuropathy [70]. PET studies confirm that minocycline can modulate microglial activity in humans, providing evidence of the biological activity of this therapy [71].

Elevated levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) observed in patients following trauma and surgery correlate with the severity of chronic pain. Cytokine-modulating therapies may help reduce excessive pain transmission. Neutralisation of TNF-α rapidly decreases pain-related activity in the brain before anti-inflammatory effects appear in the joints, indicating a central mechanism [72]. IL-1β plays a key role in initiating and maintaining pain hypersensitivity by modulating the activity of neurons and glial cells. Anti-inflammatory cytokines, such as IL-10 and TGF-β, limit neuroinflammation, reduce the activation of microglia and astrocytes, and alleviate central sensitisation and chronic pain responses [73,74,75].

Specific kinase inhibitors, such as p38 MAPK inhibitors, block the activation of microglia and neurons, thereby reducing the release of pro-inflammatory cytokines and central pain sensitisation, making them a promising therapeutic target for neuropathy and neuroinflammation [76]. Low-dose naltrexone (LDN) modulates neuroinflammation in the central nervous system, likely by inhibiting microglial activation, thereby reducing central sensitisation and chronic pain transmission [77,78].

Resolvins, derivatives of omega-3 fatty acids, effectively modulate neuroinflammation and pain hypersensitivity in models of inflammatory and neuropathic pain, making them a promising therapeutic approach for the treatment of chronic pain, with potentially fewer side effects than conventional drugs [79].

Neuromodulation is a therapeutic approach that modulates the activity of the nervous system to reduce pain, encompassing both invasive techniques, such as spinal cord stimulation (SCS), and non-invasive techniques, such as transcutaneous electrical nerve stimulation (TENS) or brain stimulation [transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS)]. Its mechanism of action involves the reduction of pain transmission, central sensitisation, and neuroinflammation, making it a promising non-pharmacological strategy for the management of postoperative pain [80].

4. Discussion

Current evidence suggests that musculoskeletal injury triggers not only tissue repair processes but also complex neuroimmune interactions. Cell damage leads to the release of DAMPs, the activation of macrophages and mast cells, and the stimulation of both the peripheral and central nervous systems. Experimental and clinical data show that these processes lead to the activation of microglia and astrocytes, increased production of pro-inflammatory cytokines, and changes in synaptic transmission in the spinal cord and brain. Neuroinflammation thus constitutes the body's dynamic response to injury, which may permanently alter the processing of pain stimuli and lead to central sensitisation.

This process plays a key role in the transition from acute to chronic pain. Persistent activation of glial cells and the release of pro-inflammatory mediators lead to excessive neuronal excitability and pathological changes in synapses. A self-sustaining neuroimmune loop is formed, in which pain signals amplify the immune response, whilst inflammatory mediators intensify pain transmission. The simultaneous increase in excitatory signals and the weakening of inhibitory ones leads to established hypersensitisation. This mechanism explains why pain can persist despite tissue healing.

Despite advances, knowledge of neuroinflammation in chronic pain remains limited. Most data come from animal models, which do not fully reflect the complexity of human pain. Direct investigation of neuroinflammatory processes in humans is difficult and relies on indirect markers, cerebrospinal fluid analysis or neuroimaging, which provide only a partial picture. Furthermore, clinical studies are characterised by high heterogeneity in both the study population and the injuries, making it difficult to establish clear-cut correlations.

Understanding the role of neuroinflammation has significant clinical implications. It enables the identification of patients at high risk of chronic pain and the development of therapies targeting central mechanisms. Modulating microglial activity, inhibiting pro-inflammatory cytokines or blocking key signalling pathways, such as caspases or MAP kinases, may reduce central sensitisation. Certain non-pharmacological approaches, including neuromodulation, also influence nervous system activity and may reduce chronic pain.

Future research should focus on developing biomarkers of neuroinflammation to enable early diagnosis, treatment monitoring and personalised therapy. Translational studies combining experimental models with neuroimaging and clinical analysis are also essential. Further clinical trials targeting the modulation of neuroinflammatory processes may lead to the development of new, effective strategies for treating chronic pain following orthopaedic injuries.

Neuroinflammation is a promising concept linking orthopaedic injury to chronic pain. It integrates immune system activation and neuronal changes, explaining the persistence of pain after tissue healing. Despite a growing body of experimental data, further clinical studies are needed to confirm these mechanisms and develop new, targeted therapies for patients with chronic pain.

5. Conclusions

Neuroinflammation links musculoskeletal injury to chronic pain by integrating immune activation and neuronal changes, leading to central sensitisation and persistent pain even after tissue healing. While experimental data support this mechanism, clinical evidence remains limited. Further research is needed to identify biomarkers, clarify human neuroinflammatory pathways, and develop targeted therapies to prevent or treat chronic pain following orthopaedic injuries.

Author Contributions: All authors have read and agreed with the published version of the manuscript.
Funding statement: The study received no financial support.
Conflict of Interest Statement: The authors declare no conflict of interest.

REFERENCES

1. Zhao, Y., Zhang, H., Li, N., Li, J., & Zhang, L. (2022). Chronic pain after bone fracture: Current insights into molecular mechanisms and therapeutic strategies. *Brain Sciences, 12*(8), 1056. https://doi.org/10.3390/brainsci12081056
2. Lafuente-Gracia, L., Borgiani, E., Nasello, G., & Geris, L. (2021). Towards in silico models of the inflammatory response in bone fracture healing. *Frontiers in Bioengineering and Biotechnology, 9*, 703725. https://doi.org/10.3389/fbioe.2021.703725
3. ElHawary, H., Baradaran, A., Abi-Rafeh, J., Vorstenbosch, J., Xu, L., & Efanov, J. I. (2021). Bone healing and inflammation: Principles of fracture and repair. *Seminars in Plastic Surgery, 35*(3), 198–203. https://doi.org/10.1055/s-0041-1732334
4. Wood, M. J., Miller, R. E., & Malfait, A. M. (2022). The genesis of pain in osteoarthritis: Inflammation as a mediator of osteoarthritis pain. *Clinics in Geriatric Medicine, 38*(2), 221–238. https://doi.org/10.1016/j.cger.2021.11.013
5. Li, M., Yin, H., Yan, Z., Li, H., Wu, J., Wang, Y., Wei, F., Tian, G., Ning, C., Li, H., Gao, C., Fu, L., Jiang, S., Chen, M., Sui, X., Liu, S., Chen, Z., & Guo, Q. (2022). The immune microenvironment in cartilage injury and repair. *Acta Biomaterialia, 140*, 23–42. https://doi.org/10.1016/j.actbio.2021.12.006
6. Ridehalgh, C., Fundaun, J., Bremner, S., Cercignani, M., Koushesh, S., Young, R., Novak, A., Greening, J., Schmid, A. B., & Dilley, A. (2025). Evidence for peripheral neuroinflammation after acute whiplash. *Pain, 166*(10), 2285–2299. https://doi.org/10.1097/j.pain.0000000000003560
7. Ridehalgh, C., Fundaun, J., Bremner, S., Cercignani, M., Young, R., Trivedy, C., Novak, A., Greening, J., Schmid, A., & Dilley, A. (2022). Does peripheral neuroinflammation predict chronicity following whiplash injury? Protocol for a prospective cohort study. *BMJ Open, 12*(12), e066021. https://doi.org/10.1136/bmjopen-2022-066021
8. Elsehrawy, G. G., Ibrahim, M. E., A Moneim, N. H., Hefny, M. A., & El Shaarawy, N. K. (2025). Transcutaneous vagus nerve stimulation as a pain modulator in knee osteoarthritis: A randomized controlled clinical trial. *BMC Musculoskeletal Disorders, 26*(1), 68. https://doi.org/10.1186/s12891-025-08288-6
9. McDermott, K., Rush, C., Pham, T., Hooker, J., Louis, C., Rochon, E. A., & Vranceanu, A. M. (2024). PTSD symptoms, pain catastrophizing, and pain outcomes after acute orthopedic injury. *Pain Medicine, 25*(12), 758–767. https://doi.org/10.1093/pm/pnae068
10. Zhang, H., Li, N., Li, Z., Li, Y., Yu, Y., & Zhang, L. (2022). The involvement of caspases in neuroinflammation and neuronal apoptosis in chronic pain and potential therapeutic targets. *Frontiers in Pharmacology, 13*, 898574. https://doi.org/10.3389/fphar.2022.898574
11. Ebersberger, A., & Schaible, H. G. (2025). Do cytokines play a role in the transition from acute to chronic musculoskeletal pain? *Pharmacological Research, 212*, 107585. https://doi.org/10.1016/j.phrs.2025.107585
12. Yoo, Y. M., & Kim, K. H. (2024). Current understanding of nociplastic pain. *The Korean Journal of Pain, 37*(2), 107–118. https://doi.org/10.3344/kjp.23326
13. Karavis, M. Y., Siafaka, I., Vadalouca, A., & Georgoudis, G. (2023). Role of microglia in neuropathic pain. *Cureus, 15*(8), e43555. https://doi.org/10.7759/cureus.43555
14. Molitoris, K. H., Huang, M., & Baht, G. S. (2024). Osteoimmunology of fracture healing. *Current Osteoporosis Reports, 22*(3), 330–339. https://doi.org/10.1007/s11914-024-00869-z
15. Ouyang, Y., Yu, M., Zhang, T., Cheng, H., Zuo, L., Liu, H., Guan, Y., Liu, A., Chen, J., He, R., Wang, S., Su, T., Tan, Y., Cu, Y., Zhang, X., Fu, X., Wang, J., Zhao, J., Peng, J., & Wang, Y. (2025). Single-cell transcriptomic landscape of sciatic nerve after transection injury. *Journal of Neuroinflammation, 22*(1), 205. https://doi.org/10.1186/s12974-025-03514-3
16. Tu, H., & Li, Y. L. (2023). Inflammation balance in skeletal muscle damage and repair. *Frontiers in Immunology, 14*, 1133355. https://doi.org/10.3389/fimmu.2023.1133355
17. Chow, S. K. H., Cui, C., Cheng, K. Y. K., Chim, Y. N., Wang, J., Wong, C. H. W., Ng, K. W., Wong, R. M. Y., & Cheung, W. H. (2021). Acute inflammatory response in osteoporotic fracture healing augmented with mechanical stimulation is regulated in vivo through the p38-MAPK pathway. *International Journal of Molecular Sciences, 22*(16), 8720. https://doi.org/10.3390/ijms22168720
18. Liu, J., Chen, Y., & Chen, G. (2025). The role and mechanisms of macrophages in chronic pain: A peripheral-to-central perspective. *Brain Research Bulletin, 229*, 111470. https://doi.org/10.1016/j.brainresbull.2025.111470
19. Harvey, A. R. (2021). Integrated neuroimmune processing of threat, injury, and illness: An ecological framework mapping social alienation onto lifetime health vulnerability. *Brain, Behavior, & Immunity - Health, 18*, 100349. https://doi.org/10.1016/j.bbih.2021.100349
20. Li, J., Wei, Y., Zhou, J., Zou, H., Ma, L., Liu, C., Xiao, Z., Liu, X., Tan, X., Yu, T., & Cao, S. (2022). Activation of locus coeruleus-spinal cord noradrenergic neurons alleviates neuropathic pain in mice via reducing neuroinflammation from astrocytes and microglia in spinal dorsal horn. *Journal of Neuroinflammation, 19*(1), 123. https://doi.org/10.1186/s12974-022-02489-9
21. García-Domínguez, M. (2025). Fibromyalgia and inflammation: Unrevealing the connection. *Cells, 14*(4), 271. https://doi.org/10.3390/cells14040271

22. Schumacher, M. A. (2024). Peripheral neuroinflammation and pain: How acute pain becomes chronic. *Current Neuropharmacology, 22*(1), 6–14. https://doi.org/10.2174/1570159X21666230808111908
23. Ayata, P., Amit, I., & Cuda, C. M. (2023). Editorial: Microglia in neuroinflammation. *Frontiers in Immunology, 14*, 1227095. https://doi.org/10.3389/fimmu.2023.1227095
24. Ustianowska, K., Ustianowski, Ł., Machaj, F., Gorący, A., Rosik, J., Szostak, B., Szostak, J., & Pawlik, A. (2022). The role of the human microbiome in the pathogenesis of pain. *International Journal of Molecular Sciences, 23*(21), 13267. https://doi.org/10.3390/ijms232113267
25. Hua, T., Yang, M., Song, H., Kong, E., Deng, M., Li, Y., Li, J., Liu, Z., Fu, H., Wang, Y., & Yuan, H. (2022). Huc-MSCs-derived exosomes attenuate inflammatory pain by regulating microglia pyroptosis and autophagy via the miR-146a-5p/TRAF6 axis. *Journal of Nanobiotechnology, 20*(1), 324. https://doi.org/10.1186/s12951-022-01522-6
26. Ackermann, P. W., Alim, M. A., Pejler, G., & Peterson, M. (2022). Tendon pain: What are the mechanisms behind it? *Scandinavian Journal of Pain, 23*(1), 14–24. https://doi.org/10.1515/sjpain-2022-0018
27. Saunders, M. N., Griffin, K. V., Kalashnikova, I., Kolpek, D., Smith, D. R., Saito, E., Cummings, B. J., Anderson, A. J., Shea, L. D., & Park, J. (2024). Biodegradable nanoparticles targeting circulating immune cells reduce central and peripheral sensitization to alleviate neuropathic pain following spinal cord injury. *Pain, 165*(1), 92–101. https://doi.org/10.1097/j.pain.0000000000002989
28. Tan, P. H., Ji, J., Yeh, C. C., & Ji, R. R. (2021). Interferons in pain and infections: Emerging roles in neuro-immune and neuro-glial interactions. *Frontiers in Immunology, 12*, 783725. https://doi.org/10.3389/fimmu.2021.783725
29. Lütolf, R., De Schoenmacker, I., Rosner, J., Sirucek, L., Schweinhardt, P., Curt, A., & Hubli, M. (2022). Anti- and pro-nociceptive mechanisms in neuropathic pain after human spinal cord injury. *European Journal of Pain, 26*(10), 2176–2187. https://doi.org/10.1002/ejp.2029
30. Lütolf, R., Rosner, J., Curt, A., & Hubli, M. (2022). Indicators of central sensitization in chronic neuropathic pain after spinal cord injury. *European Journal of Pain, 26*(10), 2162–2175. https://doi.org/10.1002/ejp.2028
31. Birklein, F., Ibrahim, A., Schlereth, T., & Kingery, W. S. (2018). The rodent tibia fracture model: A critical review and comparison with the complex regional pain syndrome literature. *The Journal of Pain, 19*(10), 1102.e1–1102.e19. https://doi.org/10.1016/j.jpain.2018.03.018
32. Guo, T. Z., Shi, X., Li, W. W., Wei, T., Clark, J. D., & Kingery, W. S. (2019). Sex differences in the temporal development of pronociceptive immune responses in the tibia fracture mouse model. *Pain, 160*(9), 2013–2027. https://doi.org/10.1097/j.pain.0000000000001592
33. Guo, T. Z., Wei, T., Li, W. W., Li, X. Q., Clark, J. D., & Kingery, W. S. (2014). Immobilization contributes to exaggerated neuropeptide signaling, inflammatory changes, and nociceptive sensitization after fracture in rats. *The Journal of Pain, 15*(10), 1033–1045. https://doi.org/10.1016/j.jpain.2014.07.004
34. Wakatsuki, K., Kiryu-Seo, S., Yasui, M., Yokota, H., Kida, H., Konishi, H., & Kiyama, H. (2024). Repeated cold stress, an animal model for fibromyalgia, elicits proprioceptor-induced chronic pain with microglial activation in mice. *Journal of Neuroinflammation, 21*(1), 25. https://doi.org/10.1186/s12974-024-03018-6
35. Chen, S. H., Huang, T. C., Wang, J. Y., Wu, C. C., & Hsueh, Y. Y. (2020). Controllable forces for reproducible chronic constriction injury mimicking compressive neuropathy in rat sciatic nerve. *Journal of Neuroscience Methods, 335*, 108615. https://doi.org/10.1016/j.jneumeth.2020.108615
36. Afshar, A., Tabrizi, A., & Shariyate, M. J. (2025). Autonomic component of carpal tunnel syndrome. *The Journal of Hand Surgery, 50*(4), 491–496. https://doi.org/10.1016/j.jhsa.2024.11.018
37. Yokoyama, T., Lisi, T. L., Moore, S. A., & Sluka, K. A. (2007). Muscle fatigue increases the probability of developing hyperalgesia in mice. *The Journal of Pain, 8*(9), 692–699. https://doi.org/10.1016/j.jpain.2007.05.008
38. Chen, G., Zhang, Y. Q., Qadri, Y. J., Serhan, C. N., & Ji, R. R. (2018). Microglia in pain: Detrimental and protective roles in pathogenesis and resolution of pain. *Neuron, 100*(6), 1292–1311. https://doi.org/10.1016/j.neuron.2018.11.009
39. Li, X., Guo, Q., Ye, Z., Wang, E., Zou, W., Sun, Z., He, Z., Zhong, T., Weng, Y., & Pan, Y. (2021). PPAR γ prevents neuropathic pain by down-regulating CX3CR1 and attenuating M1 activation of microglia in the spinal cord of rats using a sciatic chronic constriction injury model. *Frontiers in Neuroscience, 15*, 620525. https://doi.org/10.3389/fnins.2021.620525
40. Mo, Y., & Chen, K. (2023). Review: The role of HMGB1 in spinal cord injury. *Frontiers in Immunology, 13*, 1094925. https://doi.org/10.3389/fimmu.2022.1094925
41. O'Reilly, M. L., Wulf, M. J., Connors, T. M., Jin, Y., Bearoff, F., Bouyer, J., Kortagere, S., Bethea, J. R., & Tom, V. J. (2025). Microglial IKKβ alters central and peripheral immune activity at distinct time points after spinal cord injury. *Glia, 73*(8), 1746–1766. https://doi.org/10.1002/glia.70030
42. Fan, X., Ma, W., Zhang, Y., & Zhang, L. (2020). P2X7 receptor (P2X7R) of microglia mediates neuroinflammation by regulating (NOD)-like receptor protein 3 (NLRP3) inflammasome-dependent inflammation after spinal cord injury. *Medical Science Monitor, 26*, e925491. https://doi.org/10.12659/MSM.925491

43. Hains, B. C., & Waxman, S. G. (2006). Activated microglia contribute to the maintenance of chronic pain after spinal cord injury. *The Journal of Neuroscience, 26*(16), 4308–4317. https://doi.org/10.1523/JNEUROSCI.0003-06.2006
44. Li, J., Yang, Y., Zhao, C., Zhao, J., Wang, X., Ye, S., Wang, D., Zhou, C., Li, J., Wang, S., Li, K., Liu, C., He, X., & Qin, J. (2025). Microglial C/EBPβ-Fcgr1 regulatory axis blocking inhibits microglial pyroptosis and improves neurological recovery. *Journal of Neuroinflammation, 22*(1), 29. https://doi.org/10.1186/s12974-025-03362-1
45. Albrecht, D. S., Ahmed, S. U., Kettner, N. W., Borra, R. J. H., Cohen-Adad, J., Deng, H., Houle, T. T., Opalacz, A., Roth, S. A., Melo, M. F. V., Chen, L., Mao, J., Hooker, J. M., Loggia, M. L., & Zhang, Y. (2018). Neuroinflammation of the spinal cord and nerve roots in chronic radicular pain patients. *Pain, 159*(5), 968–977. https://doi.org/10.1097/j.pain.0000000000001171
46. Yamada, M., Fujita, Y., Hayano, Y., Hayakawa, H., Baba, K., Mochizuki, H., & Yamashita, T. (2019). Increased expression of fibronectin leucine-rich transmembrane protein 3 in the dorsal root ganglion induces neuropathic pain in rats. *The Journal of Neuroscience, 39*(38), 7615–7627. https://doi.org/10.1523/JNEUROSCI.0295-19.2019
47. Tao, Y. X. (2012). AMPA receptor trafficking in inflammation-induced dorsal horn central sensitization. *Neuroscience Bulletin, 28*(2), 111–120. https://doi.org/10.1007/s12264-012-1204-z
48. Jaffal, S. M. (2025). Neuroplasticity in chronic pain: Insights into diagnosis and treatment. *The Korean Journal of Pain, 38*(2), 89–102. https://doi.org/10.3344/kjp.24393
49. Gustin, S. M., McKay, J. G., Petersen, E. T., Peck, C. C., Murray, G. M., & Henderson, L. A. (2014). Subtle alterations in brain anatomy may change an individual's personality in chronic pain. *PLOS ONE, 9*(10), e109664. https://doi.org/10.1371/journal.pone.0109664
50. Labrakakis, C. (2023). The role of the insular cortex in pain. *International Journal of Molecular Sciences, 24*(6), 5736. https://doi.org/10.3390/ijms24065736
51. Peek, A. L., Leaver, A. M., Foster, S., Oeltzschner, G., Puts, N. A., Galloway, G., Sterling, M., Ng, K., Refshauge, K., Aguila, M. R., & Rebbeck, T. (2021). Increased GABA+ in people with migraine, headache, and pain conditions: A potential marker of pain. *The Journal of Pain, 22*(12), 1631–1645. https://doi.org/10.1016/j.jpain.2021.06.005
52. Créac'h, C., Henry, P., Caillé, J. M., & Allard, M. (2000). Functional MR imaging analysis of pain-related brain activation after acute mechanical stimulation. *AJNR. American Journal of Neuroradiology, 21*(8), 1402–1406.
53. Zhao, X., Xu, M., Jorgenson, K., & Kong, J. (2016). Neurochemical changes in patients with chronic low back pain detected by proton magnetic resonance spectroscopy: A systematic review. *NeuroImage: Clinical, 13*, 33–38. https://doi.org/10.1016/j.nicl.2016.11.006
54. Rosenström, A. H. C., Konsman, J. P., & Kosek, E. (2024). Cytokines in cerebrospinal fluid and chronic pain in humans: Past, present, and future. *Neuroimmunomodulation, 31*(1), 157–172. https://doi.org/10.1159/000540324
55. Bjurstrom, M. F., Giron, S. E., & Griffis, C. A. (2016). Cerebrospinal fluid cytokines and neurotrophic factors in human chronic pain populations: A comprehensive review. *Pain Practice, 16*(2), 183–203. https://doi.org/10.1111/papr.12252
56. Ohtori, S., Koshi, T., Yamashita, M., Yamauchi, K., Inoue, G., Suzuki, M., Orita, S., Eguchi, Y., Ochiai, N., Kishida, S., Takaso, M., Kuniyoshi, K., Aoki, Y., Ishikawa, T., Arai, G., Miyagi, M., Kamoda, H., Suzuki, M., Nakamura, J., Toyone, T., … Takahashi, K. (2011). Surgical versus nonsurgical treatment of selected patients with discogenic low back pain: A small-sized randomized trial. *Spine, 36*(5), 347–354. https://doi.org/10.1097/BRS.0b013e3181d0c944
57. Nagashima, H., Morio, Y., Yamane, K., Nanjo, Y., & Teshima, R. (2009). Tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6 in the cerebrospinal fluid of patients with cervical myelopathy and lumbar radiculopathy. *European Spine Journal, 18*(12), 1946–1950. https://doi.org/10.1007/s00586-009-1069-7
58. Liu, W., Li, C., Tan, F. C. K., Neo, H. J., Chan, Y. H., Low, C. M., & Lee, T. L. (2020). Cerebrospinal fluid of chronic osteoarthritic patients induced interleukin-6 release in human glial cell-line T98G. *BMC Anesthesiology, 20*(1), 69. https://doi.org/10.1186/s12871-020-00985-0
59. Loggia, M. L. (2024). "Neuroinflammation": Does it have a role in chronic pain? Evidence from human imaging. *Pain, 165*(11S), S58–S67. https://doi.org/10.1097/j.pain.0000000000003342
60. Cipriano, P. W., Yoon, D., Holley, D., Hargreaves, B. A., Carroll, I. R., Curtin, C. M., & Biswal, S. (2020). Diagnosis and successful management of an unusual presentation of chronic foot pain using positron emission tomography/magnetic resonance imaging and a simple surgical procedure. *Clinical Journal of Sport Medicine, 30*(1), e11–e14. https://doi.org/10.1097/JSM.0000000000000651
61. Hu, Y., Ma, J., Chen, B., Pang, J., Liang, W., & Wu, W. (2024). The duration of chronic pain can affect brain functional changes of the pain matrix in patients with chronic back pain: A resting-state fMRI study. *Journal of Pain Research, 17*, 1941–1951. https://doi.org/10.2147/JPR.S457575
62. Fiúza-Fernandes, J., Pereira-Mendes, J., Esteves, M., Radua, J., Picó-Pérez, M., & Leite-Almeida, H. (2025). Common neural correlates of chronic pain: A systematic review and meta-analysis of resting-state fMRI studies. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 138*, 111326. https://doi.org/10.1016/j.pnpbp.2025.111326

63. Zhao, Y., Zhang, H., Li, N., Li, J., & Zhang, L. (2022). Chronic pain after bone fracture: Current insights into molecular mechanisms and therapeutic strategies. *Brain Sciences, 12*(8), 1056. https://doi.org/10.3390/brainsci12081056
64. Aulenkamp, J. L., Malewicz, N. M., Brauckhoff, J. D., Zahn, P. K., Ebel, M., Schnitzler, R., Clever, J., Geßmann, J., Bauer, M., & Meyer-Frießem, C. H. (2022). Chronic pain following fracture-related surgery: Posttraumatic rather than postsurgical origin promotes chronification: A prospective observational study with 1-year follow-up. *Anesthesia & Analgesia, 134*(5), 974–986. https://doi.org/10.1213/ANE.0000000000005807
65. Vergne-Salle, P., & Bertin, P. (2021). Chronic pain and neuroinflammation. *Joint Bone Spine, 88*(6), 105222. https://doi.org/10.1016/j.jbspin.2021.105222
66. Chen, J., Wang, X., & Xu, Z. (2023). The relationship between chronic pain and cognitive impairment in the elderly: A review of current evidence. *Journal of Pain Research, 16*, 2309–2319. https://doi.org/10.2147/JPR.S416253
67. Meints, S. M., & Edwards, R. R. (2018). Evaluating psychosocial contributions to chronic pain outcomes. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 87*(Pt B), 168–182. https://doi.org/10.1016/j.pnpbp.2018.01.017
68. Kovačević, I., Pavić, J., Filipović, B., Ozimec Vulinec, Š., Ilić, B., & Petek, D. (2024). Integrated approach to chronic pain: The role of psychosocial factors and multidisciplinary treatment: A narrative review. *International Journal of Environmental Research and Public Health, 21*(9), 1135. https://doi.org/10.3390/ijerph21091135
69. Fetz, K., Lefering, R., & Kaske, S. (2023). Pre-trauma pain is the strongest predictor of persistent enhanced pain patterns after severe trauma: Results of a single-centre retrospective study. *Medicina, 59*(7), 1327. https://doi.org/10.3390/medicina59071327
70. Shin, D. A., Kim, T. U., & Chang, M. C. (2021). Minocycline for controlling neuropathic pain: A systematic narrative review of studies in humans. *Journal of Pain Research, 14*, 139–145. https://doi.org/10.2147/JPR.S292824
71. Ji, R. R., Nackley, A., Huh, Y., Terrando, N., & Maixner, W. (2018). Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology, 129*(2), 343–366. https://doi.org/10.1097/ALN.0000000000002130
72. Hess, A., Axmann, R., Rech, J., Finzel, S., Heindl, C., Kreitz, S., Sergeeva, M., Saake, M., Garcia, M., Kollias, G., Straub, R. H., Sporns, O., Doerfler, A., Brune, K., & Schett, G. (2011). Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. *Proceedings of the National Academy of Sciences of the United States of America, 108*(9), 3731–3736. https://doi.org/10.1073/pnas.1011774108
73. Laumet, G., Bavencoffe, A., Edralin, J. D., Huo, X. J., Walters, E. T., Dantzer, R., Heijnen, C. J., & Kavelaars, A. (2020). Interleukin-10 resolves pain hypersensitivity induced by cisplatin by reversing sensory neuron hyperexcitability. *Pain, 161*(10), 2344–2352. https://doi.org/10.1097/j.pain.0000000000001921
74. Ren, K., & Torres, R. (2009). Role of interleukin-1beta during pain and inflammation. *Brain Research Reviews, 60*(1), 57–64. https://doi.org/10.1016/j.brainresrev.2008.12.020
75. Buchheit, T., Huh, Y., Maixner, W., Cheng, J., & Ji, R. R. (2020). Neuroimmune modulation of pain and regenerative pain medicine. *The Journal of Clinical Investigation, 130*(5), 2164–2176. https://doi.org/10.1172/JCI134439
76. Ji, R. R., & Suter, M. R. (2007). p38 MAPK, microglial signaling, and neuropathic pain. *Molecular Pain, 3*, 33. https://doi.org/10.1186/1744-8069-3-33
77. Rupp, A., Young, E., & Chadwick, A. L. (2023). Low-dose naltrexone's utility for non-cancer centralized pain conditions: A scoping review. *Pain Medicine, 24*(11), 1270–1281. https://doi.org/10.1093/pm/pnad074
78. Kim, P. S., & Fishman, M. A. (2020). Low-dose naltrexone for chronic pain: Update and systemic review. *Current Pain and Headache Reports, 24*(10), 64. https://doi.org/10.1007/s11916-020-00898-0
79. Park, J., Roh, J., Pan, J., Kim, Y. H., Park, C. K., & Jo, Y. Y. (2023). Role of resolvins in inflammatory and neuropathic pain. *Pharmaceuticals, 16*(10), 1366. https://doi.org/10.3390/ph16101366
80. Penchev, P., Milanova-Ilieva, D., Gaydarski, L., Dimitrov, D., Tablov, B., Husain, N., Hyusein, R., Vladimirov, C., Mihaylova, M., Lozanov, I., Stavrev, D., Petrov, P. P., Stanchev, P., Velev, A., Ramadanov, N., & Peev, N. (2026). Efficacy of neuromodulation in postoperative acute and chronic low back pain after lumbar spine surgery: A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis and meta-regression. *Journal of Clinical Neuroscience, 144*, 111815. https://doi.org/10.1016/j.jocn.2025.111815