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PERIPHERAL MECHANISMS CONTRIBUTING TO OSTEOARTHRITIS PAIN

Delfien Syx[*,1,2], **Phuong B. Tran**[*,2], **Rachel E. Miller**[2], and **Anne-Marie Malfait**[2]

[1]Center for Medical Genetics, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium

[2]Department of Internal Medicine, Division of Rheumatology, Rush University Medical Center, 1611 W. Harrison St, Suite 510, Chicago, IL 60612, USA

Abstract

Purpose of review—Osteoarthritis (OA) is the most common form of arthritis and a major source of pain and disability worldwide. OA-associated pain is usually refractory to classically used analgesics, and disease-modifying therapies are still lacking. Therefore, a better understanding of mechanisms and mediators contributing to the generation and maintenance of OA pain is critical for the development of efficient and safe pain-relieving therapies.

Recent findings—Both peripheral and central mechanisms contribute to OA pain. Clinical evidence suggests that a strong peripheral nociceptive drive from the affected joint maintains pain and central sensitization associated with OA. Mediators present in the OA joint, including nerve growth factor, chemokines, cytokines, and inflammatory cells can contribute to sensitization. Furthermore, structural alterations in joint innervation and nerve damage occur in the course of OA.

Summary—Several interrelated pathological processes, including joint damage, structural reorganization of joint afferents, low-grade inflammation, neuroplasticity and nerve damage all contribute to the pain observed in OA. It can be anticipated that elucidating exactly how these mechanisms are operational in the course of progressive OA may lead to the identification of novel targets for intervention.

Keywords

Osteoarthritis; pain; peripheral; sensitization; inflammation; innervation

INTRODUCTION

Osteoarthritis is a major source of chronic pain worldwide

Osteoarthritis (OA) is a painful chronic disease that affects synovial joints, most commonly the knees, hips, hands, and spine. [1] The most recent update of the Global Burden of Disease figures (2013) estimated that nearly 242 million people were living with symptomatic and activity-limiting OA of the hip and/or knee. [2] Two major risk factors for

Corresponding author: Anne-Marie Malfait, MD, PhD, anne-marie_malfait@rush.edu, T: +1-312-563-2925, F: +1-312-563-2267.

*Both authors contributed equally.

OA include age and obesity. Since the population is ageing and obesity is rising, the prevalence of OA is increasing worldwide. In fact, the trends in OA Years Lived with Disability from 1990 to 2013 showed a 75% increase, the third most rapidly rising condition associated with disability, just behind diabetes (135%) and dementia (84%). [2] In the US, it is predicted that by 2030 an estimated 67 million adults will have doctor-diagnosed arthritis, compared with 52.5 million adults in 2010–2012. [3]

Pain is the defining clinical presentation of OA, and inadequate pain relief is a major reason for patients to visit a physician. [4] Largely because of pain, lower extremity OA is a leading cause of impaired mobility in older adults in the US [5], and is considered a key factor in onset of frailty in the elderly. [6] The severity of OA related pain and disability are significant predictors of risk for all-cause death (even when controlled for potential confounders such as obesity-related conditions). [7]

There is a pressing need for efficacious and safe therapies for OA pain

There are no approved and proven cures that slow, halt, or reverse the progression of joint damage in OA. [6] Ultimately, for millions of patients, OA of the knee or hip results in total joint replacement. Before that, patients are dependent on painkillers. Painful OA accounts for the majority of non-steroidal anti-inflammatory drugs (NSAIDs) use. [6] Other pharmacological treatments are available, such as intra-articular steroids, viscosupplementation, and more recently, the centrally acting selective serotonin reuptake inhibitor, duloxetine. [8] Chronic use of painkillers is associated with many safety concerns. NSAIDs, for example, are associated with clinically significant risk of gastro-intestinal and cardiovascular disease. [6] Opiates cause many serious problems, including constipation and respiratory depression. In the US, the dramatic increase in opioid prescription in the past 15 years has resulted in an ongoing health crisis due to the substantial rise in opioid addiction and abuse-related deaths. [9]

Despite the different treatment options, pain relief in OA remains largely inadequate and pain is a major factor for pursuing joint replacement surgery. [4] Unmistakably, there is an enormous need for new therapies that effectively and safely treat chronic OA pain. In recent years, the OA community was heartened by highly encouraging results from initial clinical trials with antibodies that block the biological activity of the neurotrophin, nerve growth factor (NGF), reviewed in [10,11]. Unfortunately, the occurrence of unexpected serious adverse events of unclear etiology, including rapidly progressive OA in non-target joints, put a hold on clinical trials in 2010. After evaluation by the US Food and Drug Administration (FDA), trials resumed in 2015 with a strict risk mitigation strategy in place (discussed in [10,12]). Clearly, while NGF blockade continues to hold tremendous promise, the experience with these trials also exposed a critical need for a deeper understanding of the interaction between pain pathways and structural joint pathology.

Central sensitization contributes to OA pain

OA pathology affects all joint tissues, including cartilage, subchondral bone (SCB), synovium, intra-articular fat, menisci (in the knee), ligaments, and periarticular muscles. Mechanical factors and low level inflammation affect individual joint tissues and subvert the

crosstalk between them, contributing to disease progression and pain. [13–15] However, within the concept that OA represents the failure of the joint as an organ [13,14], the structural determinants of OA joint pain remain unclear. Pain severity does not strongly correlate with radiographic joint damage, especially in knee OA. [16,17] This discordance can in part be explained by altered pain processing in the central nervous system (CNS) ("central sensitization"), which plays an important role in persistent pain in some OA patients. [18,19]. Indeed, it has been reported that signs of central sensitization are especially present in patients with high pain levels in the absence of moderate-to-severe radiographic changes. [20] Central sensitization contributes to many chronic pain states and involves plasticity in the pathways that transmit noxious signals from the periphery to the brain. As a consequence, the pain response is no longer proportionate to the initial peripheral stimulus. [21] The role of central sensitization in OA pain has been extensively reviewed elsewhere, and we refer the reader to these excellent reviews. [18,19,22]

Peripheral input from the joint is a major driver of OA pain

Quantitative sensory testing (QST) has revealed lower pressure pain thresholds (PPTs) in OA patients, both at the affected joints and in remote sites. [23] Lower PPTs at OA- affected joints are suggestive of peripheral sensitization [24], whereas lowered PPTs in remote sites are indicative for central sensitization. [23] While central sensitization clearly contributes to aspects of chronic OA pain, there is compelling clinical evidence that ongoing peripheral input from the affected joint drives OA pain. [25] Firstly, local anesthetics administered intra-articularly can alleviate knee pain. [26] Furthermore, peripherally restricted antagonism of NGF with neutralizing antibodies has pronounced analgesic effects in OA. [25] Finally, total joint replacement, which removes peripheral nociceptive inputs, results in pain relief in the majority of cases [4,27] and is associated with a reversal of signs of central sensitization, including in the brain. [28,29]

Thus, strong clinical evidence suggests that OA pain and sensitization are largely driven by peripheral input, even at late stages of the disease. Therefore, in order to develop more efficacious analgesics for OA pain, it is critical that we elucidate its peripheral neuronal substrates and associated mechanisms. Since animal models have been instrumental in our current understanding of peripheral mechanisms that drive pain in OA, we briefly summarize the most widely used experimental models for studying OA pain. Then, we provide a narrative review of the current knowledge of peripheral mechanisms contributing to joint pain in OA, focusing on findings from animal models published within the last 5 years. We searched PubMed using a combination of the following terms "osteoarthritis", "mechanisms", "peripheral", "pain", "innervation", and "animal models".

PRECLINICAL MODELS FOR THE STUDY OF OA PAIN

In laboratory animals, experimental OA can be induced through a variety of methods; for example, OA can occur spontaneously or it can be induced surgically, chemically, genetically, or through mechanical loading (reviewed in [30,31]). Such models provide powerful tools to study OA pathogenesis and to evaluate the effects of targeted therapeutic interventions. [32] OA models have been mostly used to explore pathogenesis of structural

damage, but they can also be used to study pain behaviors and the neurobiology of pain associated with OA. For the study of OA pain, the most commonly used model is the monosodium-iodoacetate (MIA) model [33], in which MIA is injected intra-articularly, most often into the knee, but also into the hip or ankle of rats, mice, or guinea pigs. [34] This results in chondrocyte death and leads to rapidly progressive joint damage and pain, which occurs in a dose- dependent manner. [35] In the collagenase model, intra-articular delivery of collagenase causes articular instability that is associated with pain. [36]

In more recent years, there have been efforts to model OA pain using translationally more relevant triggers. These models include obesity-related OA induced by high-fat diet [37] and various surgical methods to destabilize the knee, such as destabilization of the medial meniscus (DMM), medial meniscal tear (MMT), partial (PMX) or complete (MNX) medial meniscectomy and anterior cruciate ligament transection (ACLT).

In all these models, several distinct pain-related behaviors have been reported, including evoked pain responses to external mechanical and thermal stimuli, diminished grip strength, weightbearing deficits, ongoing pain, and altered gait. (reviewed in [38])

PERIPHERAL MECHANISMS OF OA PAIN

Nociception is the process by which intense chemical, thermal, or mechanical stimuli are detected by specialized peripheral nerves, called nociceptors. [39] The cell bodies of nociceptors are clustered in dorsal root ganglia (DRG), and extend one axon toward the periphery (for example, to the joint) and the other one toward the dorsal horn of the spinal cord, where a synapse occurs and information is transmitted to the higher regions of the CNS. Under normal conditions, nociceptors, which comprise medium-sized myelinated Aδ-fibers and slow-conducting small unmyelinated C-fibers, are exclusively excited by stimuli in the noxious range. [39] In pathological conditions, such as in inflammation, alterations in the pain pathway lead to hypersensitivity, such that painful stimuli elicit exaggerated pain (referred to as *hyperalgesia*) and innocuous stimuli such as light touch are perceived as painful (*allodynia*).

Experimental evidence for peripheral sensitization in OA

In experimental OA models, there is ample evidence for peripheral sensitization. Firstly, behavioral testing reveals local hypersensitivity, such as knee hyperalgesia, which has been detected after DMM [40], after PMX [41], and in the MIA model [42]. Evaluation of pain-related behaviors is one way of determining sensitization, but sensitization of joint-innervating afferents can be confirmed by recording or imaging of these nerves. *In vivo* electrophysiology studies in rat MIA have shown that the firing rate of C and Aδ afferents was increased in response to both non-noxious and noxious rotation of the knee joint [43], and the mechanical threshold of firing in response to rotation was decreased [44]. We have recently used a newly developed *in vivo* calcium imaging technique [45], which is complementary to electrophysiology, in order to image calcium mobilization responses in hundreds of DRG neurons simultaneously while applying mechanical stimuli to the knee joint of live, anesthetized mice 8 weeks after DMM or sham surgery [46]. We found that increased numbers of small-to-medium sized DRG neurons responded to mechanical stimuli

in DMM mice. These sizes are consistent with the size of the cell bodies of C and Aδ fibers, which include both the nociceptor and C-low threshold mechanoreceptor (C-LTMR) populations. [47,48] While the number of responding neurons is increased after DMM, the magnitude of the response is similar in sham and DMM mice, suggesting that peripheral sensitization occurs through recruitment of additional nociceptors as opposed to modulating the intensity of the response of individual neurons. These newly recruited neurons may be 'silent nociceptors' that have become sensitized to mechanical forces, and they may also be nociceptors that have become polymodal, such that they now respond to mechanical forces in addition to thermal or chemical stimuli. [49–51] Our recent observation that chemogenetic silencing of NaV1.8 positive neurons (which express the voltage-gated sodium channel, NaV1.8, and comprise the majority of C and Aδ nociceptors) reversed mechanical allodynia 8 weeks after DMM [40], further indicates that this specific subpopulation mediates mechanical hypersensitivity after DMM surgery.

These observations in experimental models indicate that nociceptors in the OA joint are sensitized, which prompts obvious questions that may be instrumental in understanding mechanisms of peripheral sensitization in OA. These questions are: (1) which are the molecular and cellular mediators that contribute to sensitization of peripheral afferents; and (2) which joint afferents are involved, *i.e.*, where in the joint are they located, and what are the structural and functional alterations in the innervation of OA joints? Current knowledge on these topics is discussed below.

1. Sensitization of afferent neurons in the OA joint—Current evidence supports the concept that OA pain is generated and maintained through continuous peripheral nociceptive input from the joint. It is, therefore, pivotal to define which mediators contribute to sensitization of joint nociceptors.

1.1 Nerve growth factor: NGF is a neurotrophic factor essential for survival of sensory and sympathetic neurons during development. In adults, however, its function changes and NGF plays a significant role in nociceptor sensitization after tissue injury, mainly through its high- affinity cognate receptor, tropomyosin-related kinase (Trk)A. [52] NGF-TrkA signaling causes sensitization of the heat-sensitive ion channel, TRPV1, and also drives transcriptional changes in nociceptors, resulting in altered expression of ion channels, neuropeptides and receptors. [52,53] As such, the pathway is critical in driving acute and chronic pain. [53]

In human subjects, subcutaneous or intramuscular injection of NGF induces local hyperalgesia. [54,55] In two rat OA models, MNX and MIA, NGF administered into the knee produced a prolonged augmentation of weightbearing asymmetry compared to NGF injection in non-OA knees. [56] NGF upregulation coincides with pain behaviors in several experimental models of OA. [57–59] In human OA, NGF levels are increased in synovial fluid [60] and synovial NGF expression is associated with pain. [61]

Such observations underscore that treatments aimed at blocking NGF-induced hypersensitivity may improve OA pain, as was indeed found in ongoing clinical trials. [10,11]

1.2 The role of low-grade inflammation and innate immunity in OA pain: In recent years, low-grade inflammation has been increasingly implicated in OA pathogenesis. [62] Synovitis, as well as pro-inflammatory cytokines and adipokines in joint tissues have all been associated with disease progression. [63] The innate immune system is key for initiation and perpetuation of low-grade inflammation and may represent a self-sustaining cycle that initiates and perpetuates joint damage, *e.g.*, after joint injury [64]. This may be significant for nociceptor sensitization and pain generation, because in the course of progressive OA pathology, joint nociceptors are exposed to their changing micro-environment. Emerging evidence indicates that nociceptors express receptors for many inflammatory mediators, which may excite and sensitize them. [65] Below, we discuss the main categories of these potential pro-algesic inflammatory molecules, present in OA joints. Identifying their precise temporospatial role in OA joint pain may represent an important step toward identifying new therapeutic strategies.

1.2.1 Damage-associated molecular patterns: Trauma and microtrauma to joint tissues can occur as a consequence of injury or ageing and result in the release of damage-associated molecular pattern proteins (DAMPs). Sources of DAMPs in OA include breakdown products from extracellular matrix proteins (*e.g.*, fibronectin), intracellular alarmins released by stressed or dying cells (*e.g.*, S100A8/9) or exudation of plasma proteins (*e.g.*, α2-macroglobulin). [66,67] DAMPs interact with pattern recognition receptors (PRRs) to trigger an innate immune response resulting in low-grade inflammation through the release of pro- inflammatory cytokines and chemokines. [67,68] Recently, it has been demonstrated that sensory neurons also express PRRs, including Toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE); therefore, PRRs may directly contribute to pain. [69–71]

A number of studies highlight a potential role for specific DAMPs in OA pain. S100A8 and α2-macroglobulin have been detected in OA joints [66], and can directly excite the nociceptor population of cultured murine DRG neurons and stimulate the release of the pro-algesic chemokine, CCL2, in a TLR4-dependent manner. [72] While these findings suggest that activation of TLR4 may promote nociception, *Tlr4*−/− mice were not protected from mechanical allodynia after DMM, suggesting the contribution of other pathways to pain in this model. [72] Studies in primary DRG neurons have shown that HMGB-1 can drive calcium mobilization and increased

excitability in primary afferent neurons in a RAGE-dependent fashion [71,73]. Intra-articular injection of HMGB-1 into murine ankle joints caused mechanical hypersensitivity. [74] In human knee OA, increased synovial fluid HMGB-1 levels were associated with severity of synovitis and pain. [75] Since turnover of the extracellular matrix and damage are hallmarks of OA pathology, it will be crucial to study the effects of DAMPs on nociceptor sensitization in order to define pain pathways in the joint.

1.2.2 Cytokines and chemokines: A broad range of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α), have been detected in human and experimental OA joints. [76] These cytokines can contribute to pain generation and nociceptor sensitization, either indirectly through promoting inflammation (*e.g.*,

prostaglandin release) or directly, through sensitization of sensory neurons, which express cytokine receptors. (for a detailed review, see [77]) Measuring action potentials following direct injection of cytokines into the joint cavity of healthy rats demonstrated sensitization of Aδ fibers by TNF-α [78] and C-fibers by TNF-α [78], IL-6 [79], IL-1β [80] or IL-17A [81], in response to innocuous or noxious mechanical stimuli. Since cytokines can be targeted with monoclonal antibodies, several ongoing clinical trials are evaluating their analgesic effects in knee and hand OA, but results have been largely disappointing until now. [82]

Solid evidence supports a contribution of chemokines and their receptors to peripheral sensitization. Chemokines control trafficking of immune cells, but their participation in induction and maintenance of pain is not restricted to their chemotactic activities. [83] Peripheral sensory neurons can be directly activated by chemokines. CCL2 (also known as MCP-1), in particular, has been shown to play a key role in the maintenance of chronic pain in experimental OA. Eight weeks after DMM, CCL2 and its receptor, CCR2, were transiently upregulated in DRG neurons, coinciding with the development of movement-provoked pain and maintenance of mechanical allodynia. *Ccr2*−/− mice were protected from chronic pain associated with OA through 16 weeks after surgery. [84] An independent study confirmed a delayed onset of pain in *Ccl2*−/− and *Ccr2*−/− mice following DMM. [85] Pharmacological blockade of CCR2 using a selective small-molecule CCR2 antagonist following DMM surgery reversed weightbearing deficits, with sustained improvement even after treatment was ceased. [86]

Levels of CCR2 ligands (CCL2, CCL7 and CCL8) but not CCR5 ligands (CCL3, CCL4 and CCL5) are all elevated in synovial fluid of OA patients [87], and CCL2 synovial fluid levels have been shown to correlate with symptom severity. [88] In two separate patient cohorts, associations were reported between synovial mRNA for *CCR7* and its ligand, *CCL19*, and severity of knee symptoms [89,90]. Furthermore, expression of CCR7 in the synovial membrane was higher in patients undergoing meniscal arthroscopy or total knee replacement than in asymptomatic controls. [91] *Ccr7*−/− mice showed delayed pain behaviors after DMM surgery compared to wild-type mice. This finding paralleled attenuated subchondral bone changes and perhaps suggests a role for CCR7 in early development of functional deficits and bone changes following posttraumatic injury. [91]

Besides the CCR2 and CCR7 pathways, there is also experimental evidence for a role for fractalkine (CX3CL1) and its receptor (CX3CR1) in the development of chronic pain in several nerve injury animal models. [92] Fractalkine is a unique transmembrane protein expressed by neurons, and enzymatic cleavage of the protein releases a chemotactic fragment. [92] After DMM surgery, fractalkine release by DRG neurons is upregulated in the late phase of the model, and this timing correlates with the development of microgliosis in the dorsal horn, where microglial cells express CX3CR1. [93]

1.2.3 OA-associated immune cell infiltration and activation: Studies are increasingly reporting the presence of inflammatory cells in the synovium and infrapatellar fat pad of OA patients and experimental models, mainly macrophages, mast cells, and T lymphocytes. [15,94–97]

These inflammatory cells may contribute to synovitis and promote joint damage [98], but very little is known about their role in joint pain. A recent study used an imaging technique to detect activated macrophages *in vivo* in 50 OA patients, by using the molecular imaging agent, ^{99m}Tc-EC20 (Etarfolatide), which is specific for glycosylphosphatidylinositol-anchored folate receptor β on activated, but not resting, macrophages or other immune cells. [99] Activated macrophages were present in the majority (76%) of knees, and they were significantly associated with severity of knee pain and with radiographic OA severity. Furthermore, joint pain at fingers, wrists, ankles and great toes was also positively associated with the presence of activated macrophages at these sites. [99] In addition, a soluble biomarker of macrophage activation, CD14, in synovial fluid and serum has been associated with knee OA pain. [100]

Virtually nothing is known about the contribution of joint macrophages to pain in experimental OA models. However, macrophage infiltration has been demonstrated in DRGs, and this may represent an additional facet of peripheral sensitization. [101] After DMM surgery, upregulation of CCL2/CCR2 results in infiltration of macrophages into the knee-innervating DRG, and this correlates with development of persistent pain. *Ccr2−/−* mice show less macrophage infiltration into the DRG than wild-type mice, consistent with the lack of persistent pain in these mice. [84] Macrophage infiltration has also been shown in the inflammatory antigen- induced arthritis (AIA) model in rats. [102,103] It has been proposed that depending on the activation state of macrophages, they can exert different functions, ranging from sensitization to destruction of DRG neurons. [102]

Recent work has focused on a potential contribution of mast cells to OA pain. Mast cells can both release and respond to NGF. [104] Increased TrkA receptor signaling in MIA-induced OA in transgenic mice harboring a TrkA gain-of-function mutation resulted in increased pain accompanied by higher numbers of leukocytes, macrophages, and mast cells in the synovial fluid. [105] Interestingly, a close anatomical connection was observed between CD117+ mast cells and peptidergic C- fibers in the synovium, suggesting a role for cell-to-nociceptor communication in OA pain. [105] In human OA synovium, prevalence of mast cells is relatively high, but not associated with self-reported knee pain. [106] However, measures of sensitization were not included in this study and further research is necessary to examine the role of these cells in clinical OA. Clearly, this is an exciting avenue of new research, which may reveal new targets for OA pain.

It was recently reported that immune cells can release serine proteinases such as neutrophil elastase, which can activate proteinase activated receptor 2 (PAR2) on the terminals of joint afferents, triggering joint inflammation and pain. [107] Prophylactic treatment with inhibitors of neutrophil elastase prevented MIA-induced inflammation and mechanical allodynia. [108]

1.2.4 Neuropeptides: Several experimental findings implicate the neuropeptide, calcitonin gene- related peptide (CGRP), in peripheral mechanisms of OA pain. (reviewed in [109]) In the joint, CGRP is released from the peripheral terminals of nociceptors and it can act on its receptor expressed on various cellular targets, including on vascular cells within the synovium, resulting in vasodilation and neurogenic inflammation, and on peripheral

terminals of sensory neurons, resulting in sensitization of joint afferents. Injecting CGRP into rat MIA knees increased mechanical sensitivity in a greater proportion of joint nociceptors than in saline-treated rats, and local blockade of endogenous CGRP reversed enhanced joint nociceptor responses in rat MIA and MMT. [110] Synovial expression of CGRP was associated with pain in knee OA patients. [111]

Although CGRP inhibition showed promising analgesic effects in animal models of OA [112] [113], a neutralizing monoclonal antibody failed to reduce signs and symptoms of knee OA in a phase 2 clinical trial. [114]

2. Innervation of the OA joint—Except for the aneural cartilage, all joint structures are innervated by sensory afferents (80% of which are nociceptors) and sympathetic neurons. Light and electron microscopy studies have shown afferents in the capsule, ligaments, menisci, periosteum and SCB. [115–119]

2.1 Innervation changes in OA: Elucidating which structures in an OA joint might contribute to sensitization and pain will require in-depth description of its sensory innervation. Literature on neuroanatomical changes in sensory innervation of the different articular structures in OA is scant. Non-inflamed synovium from human knees obtained during total knee arthroplasty exhibited a dense vascular and neuronal network consisting of CGRP+ C-fibers, and tyrosine hydroxylase (TH)+ nerves, while inflamed synovium showed a significant decrease of nerve fibers, potentially caused by inflammatory destruction. [120] TH is a marker for sympathetic nerves [121], but also for a specific class of C- fibers that normally respond to low-threshold stimuli, C-LTMRs [47], which have been shown to also express the mechanosensitive receptor, Piezo2 [47,122]. C-LTMRs have been proposed to contribute to light touch under normal conditions [123–127] and to touch hypersensitivity after injury [126,128,129]. Nothing is known about the role of this specific neuronal subpopulation in OA pain.

Very few studies have examined innervation changes in animal models of OA. Two studies in the collagenase-induced model reported either a transient [130] or a permanent [131] decrease in sensory innervation in the synovium, particularly CGRP+ and substance P+ (*i.e.*, peptidergic) fibers.

In addition to these studies suggesting decreased synovial innervation, there is also preclinical evidence for ectopic sprouting of sensory and sympathetic nerves in arthritic joints. Injection of complete Freund's adjuvant into the knee resulted in robust pain-related behaviors, associated with formation of neuroma-like structures by CGRP+, NF200+, and TH+ nerve fibers in the synovium and periosteum. [132,133] While these neuroma-like structures have not yet been demonstrated in experimental models of OA, there are several reports of aberrant OA joint innervation that may contribute to pain. In particular, vascular channels that breach the osteochondral junction have been observed, both in human joints [134] and in experimental OA [135], and these channels may contain sensory neurons and therefore be a potential source of peripheral sensitization and pain. [134] In human joints, vascular penetration and nerve growth have been described in the meniscus [136], osteophytes, and SCB [137].

While detailed information on innervation of the OA knee is lacking, published findings summarized above indicate that extensive remodeling of sensory innervation is an integral part of the OA disease process. This neuroplasticity occurs in different joint tissues, including synovium, SCB, meniscus, and maybe even articular cartilage but the factors that mediate these processes need further clarification. One explanation is that NGF contributes to nerve growth or sprouting, since, in addition to its role in sensitization, NGF is capable of inducing nociceptor sprouting. [53] Thus, the remarkable analgesic effects of NGF-TrkA blockade may in part be due to reduced nerve growth in the OA joint, but this has not been demonstrated.

2.2 Contribution of neuronal degeneration to OA pain: In addition to nociceptive pain and peripheral sensitization in OA, there is increasing evidence for a neuropathic component of OA pain. A recent systematic review estimated the prevalence of neuropathic pain in knee and hip OA to be around 23%. [138]

Studies in collagenase- and MIA-induced OA in rats demonstrated that sensory nerves innervating the OA joint express the neuronal damage markers, activating transcription factor 3 (ATF3) or neuropeptide Y, in the DRG. [35,139–141] It is not clear, however if the observed nerve damage is part of OA pathology or a neurotoxic effect of MIA, and therefore validation in other OA models is necessary. [35]

The chemical mediators responsible for OA neuropathy are unknown, but the lipid mediator, lysophosphatidic acid (LPA), has recently emerged as one potential candidate. Intra-articular injection of LPA into rat knees initiated afferent demyelination, reduced conduction velocity, increased ATF3 expression, and resulted in weightbearing deficits. [142] MIA-treated rats also showed signs of demyelination and nerve damage with concomitant pain, which were attenuated by early treatment with the LPA receptor antagonist, Ki-16425. [142]

CONCLUSION AND FUTURE RESEARCH AVENUES

Peripheral and central mechanisms contribute to OA pain. Strong clinical evidence exists that ongoing peripheral input from the affected joint drives pain and central sensitization in the majority of OA patients. Therefore, in-depth understanding of the molecular, cellular, and neurobiological mechanisms that maintain peripheral nociception and sensitization in OA will be critical for identifying novel targets for intervention. Recent years have witnessed many exciting new discoveries in animal models of OA, all pointing to evidence that several interrelated factors, including joint damage, structural reorganization of joint afferents, low-grade inflammation, locally released neuropeptides, neuroplasticity as well as nerve damage all contribute to the pain observed in OA. It can be anticipated that elucidating the exact temporospatial characteristics of these different mechanisms, and how they are operational in different subsets of OA, will require in-depth preclinical and clinical research but ultimately may lead to development of targeted therapies.

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