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Therapeutic options for targeting inflammatory osteoarthritis pain

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Abstract

Pain is the major symptom of osteoarthritis (OA) and is an important factor in strategies to manage this disease. However, the current standard-of-care does not provide satisfactory pain relief for many patients. The pathophysiology of OA is complex and its presentation as a clinical syndrome is associated with pathologies of multiple joint tissues. Inflammation is associated with both OA pain and disease outcome and is therefore a major target to treat OA and OA pain. Unlike TNF inhibitors and IL-1 inhibitors, established drugs such as corticosteroids and methotrexate can reduce OA pain. Although central nociceptive pathways contribute to OA pain, crosstalk between the immune and nociceptive neurons is central to inflammatory pain; therefore, new therapies might target this crosstalk. Indeed, newly identified drug targets including neurotrophins and the GM-CSF-CCL17 axis offer the hope of better results, but require clinical validation.

Introduction

Osteoarthritis (OA) is a substantial morbidity for individuals and an increasing problem for health care services. The symptoms of OA can be functional but manifest predominantly as pain, and as such the clinical management of OA is dominated by pain relief and pain management. In the US alone, persistent pain (including neuropathic pain in OA which develops when the nociceptive nerve fibers are triggered by inflammation and mechanical factors) is estimated to affect ~37% of the population [1]. Current clinical strategies are inadequate for many OA patients, with muscle strengthening and exercise often under-utilised [2] and the few pharmacological options that are available carry substantial potential for adverse effects, especially in the elderly. Examples include acetaminophen-induced hepatotoxicity, nonsteroidal anti-inflammatory drug (NSAID)-induced gastrointestinal toxicity and opioids-induced risk of falls, fractures, and delirium [3].

The pathophysiology of OA is complex as what is effectively a clinical syndrome involves pathology in multiple joint tissues, including cartilage, subchondral bone and synovium. Therefore, established OA is now considered to be a whole-organ structural disease [4]Joint inflammation is common in OA [5,6] and can cause pain, but new data, principally regarding the efficacy of nerve growth factor (NGF) blockade, has led to an increased focus on peripheral nociception. Furthermore, advances in our understanding of the inter-relationship of pain and inflammation are providing new therapeutic targets to alleviate OA pain. OA pain might be caused by a variety of mechanisms, including activation of nociceptive pathways by NGF and other mediators, inflammation, direct effects of cytokines and chemokines on neurons, or as a result of infiltration of the spinal cord by immune cells [7-9].

Clinical trials of drugs that interfere with these pathways provide interesting insights into the mechanisms of OA pain. Success with intra-articular injection of glucocorticoids [10] for example, supports the idea that clinicians should treat patients with OA by treating inflammation, although not all studies could confirm the positive effect of this approach [11]. Therapies that target individual pro-inflammatory mediators, such as TNF [12,13] or interleukin 1β (IL-1β) [14,15] have mostly failed to reduce

the symptoms of OA. Given the risks associated with long-term broad spectrum anti-inflammatory therapy, alternative analgesic methods are being tested, including those that target peripheral nociceptive pathways.

Given the growing burden of symptomatic OA and the requirement for new medicines and strategies to safely reduce the clinical symptoms of OA and potentially protect the joints against progressive destruction, this Review describes these new concepts and pharmacological attempts to treat OA by targeting pain and inflammation.

Pain mechanisms

Pain (dolor) was recognized as one of the cardinal signs of inflammation during the time of Celsus in the 1st Century AD. However, pain is a complex phenomenon potentially involving psychosocial and biological mechanisms and chronic pain is dependent on peripheral, spinal and central neurological pathways [9,16]. Nociception is the process by which chemical, mechanical or thermal stimuli are detected by specialized peripheral neurons called nociceptors [17]. The cell bodies of nociceptors are clustered in dorsal root ganglia (DRG) and extend one axon towards the periphery (for example, to the joint) and the other one towards the dorsal horn of the spinal cord resulting in transmission of information to higher regions of the central nervous system (Figure 1). In inflammatory conditions, painful stimuli can cause neuronal hypersensitivity (hyperalgesia) and otherwise innocuous stimuli such as touch can be perceived as painful (allodynia)[17].

Acute inflammation and associated nociceptive pain is considered to be a protective response to prevent behaviours that result in tissue injury and can initiate tissue repair mechanisms [18]. However, many injurious stimuli can trigger persistent inflammation locally or centrally in DRGs or the spinal cord. In this context, pro-inflammatory mediators can activate and sensitize nociceptors causing chronic pain in diseases such as rheumatoid arthritis (RA), periodontitis and inflammatory bowel

disease [7,8,19]. Importantly, the immune and nervous systems can recognize and respond acutely to these triggers in a coordinated manner and thereby can regulate each other [20,21]. A wide variety of immune cells can cause changes in sensory neurons through the production of pro-inflammatory mediators like e cytokines and chemokines, leading to inflammatory pain; conversely, monocytes/macrophages may also contribute to the resolution of inflammatory pain via a mechanism dependent on IL-10 signalling in dorsal root ganglia. [22,23]. In addition, evidence indicates that inflammation is involved in neuropathic pain [24] and the function of neurotrophins such as NGF and brain-derived neurotrophic factor [25-29]. Bi-directional cross-talk between the immune system and nociceptors therefore seems to be fundamental to the development of chronic and acute inflammatory pain (Figure 2a).

Aside from immune cells, other non-neuronal cells can also affect pain sensation, including glial, epithelial and mesenchymal cells [30]. In response to damage, these cells can release neuromodulatory mediators adjacent to nociceptors that can either enhance or dampen pain [30]. Nociceptors in turn can release neuropeptides and neurotransmitters that, for example, modulate the function of innate and adaptive immune cells (Figure 2a) [1,20,31-40].

Inflammation associated with tissue damage can result in the release of a wide array of neuromodulatory mediators, such as cytokines and eicosanoids, for example, prostaglandin E_2 that can be produced by a wide variety of immune and non-immune cells. These mediators can engage signalling cascades which can reduce the threshold for nociceptor neurons to fire action potentials for key neuronal receptors such as TRPV1 and Nav1.8, leading to hyperalgesia (Figure 2b) [40]. DRG neurons that mediate pain signalling under physiological conditions express a number of different types of receptors (such as ion channels and G-protein coupled receptors) that can enhance neuronal excitability [41] (Figure 2b). Cytokines were once thought to activate nociceptors only indirectly via the release of neurostimulators such as NGF, prostaglandins, kinins and amines from non-neuronal cells; however, some cytokines (e.g. TNF) can sensitize nociceptors directly if the specific receptor is expressed (Figure 2b) [33,35, 7]. Nociceptive nerve terminals, in turn, can secrete substance P and

calcitonin gene related peptide (CGRP), which can promote vasodilation and extravasation of immune cells [30]. Although the contribution of these mechanisms to pain probably varies between patients, in general the bidirectional cross-talk between the immune and nervous systems could be utilized to increase the number of clinical options for alleviating pain (Figure 2a).

Pain and inflammation in OA

Inflammation is common in OA joints, with detection increased if modern imaging modalities (MRI and ultrasound) or synovial biopsy are used (reviewed elsewhere [42,43]). Imaging-detected synovitis is often associated (although not necessarily causatively) with both pain and structural progression and subsequent joint replacement [44,45]. Compared with a primary inflammatory arthritis such as RA, inflamed OA synovial tissue is populated by fewer immune cells, cytokines and other inflammatory mediators [46,47]. However, the innate immune system, including the complement and pattern-recognition receptor systems as well as the pro-inflammatory state associated with obesity may all contribute to OA synovial inflammation [42,48].

OA pain is driven by stimulation of nociceptive nerve fibers related to mechanical factors, as illustrated by eight-bearing aggravation of pain [9], as well as by mediators of inflammation [16]. Inflamed OA tissues can express proalgesic molecules such as NGF, bradykinin receptors and tachykinin [49,50].

MRI studies of OA have reported an association between synovitis and pain [51-53] , suggesting that OA pain is driven by inflammation, but not all studies could confirm this [54]. Traditional OA structure-pain studies using radiographical data have not been able to correlate pain and structural damage [55], but one study of individuals with two painful knees showed some association [56] , probably as this study could take into account differing pain perception between individuals, something that cannot be easily done in studies of individual knees. MRI studies have demonstrated associations

between pain on the one hand and synovitis [57], cartilage loss [58] and osteophyte formation [58] on the other, but the strength of these associations is relatively weak.

Given the complexity of measuring pain as a single construct, and the fact that neuroplastic changes occur in the peripheral and central nervous system resulting in pain sensitisation impacting the patient's experience of pain [59], these somewhat conflicting data are not particularly surprising. As a further example of this complexity, pain in any given joint might be secondary to extra-articular features, such as bursitis or tendinopathy, for which imaging may not have been optimised to detect. Furthermore, pathogenetic mechanisms outside the joint could drive OA pain, as leukocytes trafficking into the DRG and spinal cord may actively contribute to nociceptive hypersensitivity [60,61].

Unfortunately, the OA research field is somewhat divided into the study of disease modification, on the one hand, and pain on the other [16]. It should be noted that the value of disease modification for the OA patient remains unproven until there is evidence that disease-modifying anti-OA drugs (DMOADs) can improve symptoms and/or function. One future approach could be to split the therapeutic options based on the possible effects on different tissues and disease mechanisms (cartilage, subchondral bone, synovitis and central pain regulation) [62]. Importantly, in our view, inflammation in the joints might contribute to both pain development and joint pathology in a particular subset of OA (the patients with prominent synovitis), implying that anti-inflammatory strategies could alleviate both pain and improve joint function in a subset of patients, but therapeutic strategies might differ between patients based on underlying disease mechanisms.

Targeting inflammation to treat OA pain

NSAIDs and glucocorticoids

The efficacy of two existing OA therapies supports the notion that inflammation drives pain in at least some patients with OA. As shown in multiple OA studies, both NSAIDs [63] and intra-articular

glucocorticoids [10] have analgesic effects, albeit these effects are modest for NSAIDs and often short-lived for intra-articular glucocorticoids. One study did not show a significant effect of intra-articular glucocorticoid (triamcinolone) treatment on knee pain, although there was greater cartilage volume loss after two years of triamcinolone treatment (40 mg/3 months) compared to placebo treatment; the usual short-term benefits of intra-articular glucocorticoid treatment were probably missed in this study [11]. Low dose (5 mg/day) oral glucocorticoids did not improve pain measured by visual analogue scale (VAS) in patients with hand OA [64], possibly reflecting a need for higher concentrations of drug in the target tissue. Indeed, intramuscular glucocorticoids (40 mg triamcinolone), with probably a higher peak dose than low dose prednisolone have been shown to reduce resting hip pain measured by VAS in OA patients [65]. Baseline synovitis does not consistently predict treatment response to intra-articular glucocorticoids. In an observational study of intra-articular glucocorticoids (80 mg methylprednisolone acetate) with baseline contrast-enhanced MRI, baseline synovitis did not predict pain changes measured by VAS and Knee Injury and OA Outcome Score after treatment[66], but another study using the same intra-articular glucocorticoid dose, MRI synovitis was predictive of pain reduction as shown by the decrease in Knee Injury and Osteoarthritis Outcome Score [67] after treatment . In a pooled analysis of three trials, inflammation at baseline was associated with improvement in pain measured by Average Daily Pain (ADP)-intensity score after treatment with a triamcinolone extended-release product [68]. Together, these data suggest that glucocorticoids can reduce OA pain, particularly at relatively high concentrations.

Colchicine

Crystals are thought to be a major driver of inflammation in OA, and are frequently found in cartilage in more advanced structural disease [69]. Basic calcium phosphate crystals, of which the hydroxyapatite form is most common, occur in ~70% of patients with OA patients and the concentration of these crystals correlates with the extent of cartilage degradation [69,70]. Crystals are a 'danger signal' that can

activate inflammatory cells and stromal cells to promote the production of mediators of inflammation and tissue destruction [71]. However, a randomized controlled trial (RCT) of colchicine (a mitotic spindle inhibitor with effects on neutrophil motility and which is commonly used for the inflammation and pain associated with gout) did not reduce pain in patients with knee OA [72].

DMARDs

Synthetic and biologic DMARDs have revolutionized the treatment of chronic inflammatory arthritis, reducing the symptoms and structural damage [73]. However, the benefits of some of these drugs in OA are questionable.

Synthetic DMARDs. Hydroxychloroquine, which functions in part by blocking activation of Toll-like receptor 7 (TLR7) and TLR9 [74] , has been used to treat inflammatory OA for many years. However, two RCTs of hydroxychloroquine did not reduce pain in hand OA trials [75,76], and ultrasound-detected synovitis did not predict treatment response [75].

Methotrexate is the most commonly used drug to treat RA and has pleiotropic anti-inflammatory and immunomodulatory effects [77,78], including a reduction in the number of macrophages in the synovium and reduced synovial expression of the adhesion molecules ICAM-1 and VCAM-1 [77]. Methotrexate might therefore inhibit the migration of monocytes and other immune cells into these tissues which could be a mechanism to limit OA pain also. Indeed, an open-label study of 31 patients with inflammatory OA showed that 43% of patients achieved ≥30% reduction in pain at 24 weeks, as measured by visual analogue scale (VAS) [79]. Interestingly, in this study correlations were not detected between changes in ultrasound-detected synovitis and pain scores at 24 weeks. Although these data require confirmation from large RCTs, they support the hypothesis that patients with OA might benefit from anti-inflammatory therapies, but the mechanism of this action might not be via an effect on synovitis. The Pain Reduction with Oral Methotrexate in knee Osteoarthritis (PROMOTE) trial was set

up to confirm these findings with a multi-centre randomized, double-blind, placebo-controlled trial of 155 patients with symptomatic knee OA [80]. Preliminary results from this trial show that at average knee pain (as measured by numerical rating scale) was 6.2 in the placebo group and 5.1 in the methotrexate group at 6 months, with a baseline adjusted treatment difference of -0.83 points (95% CI -1.55 to -0.10; p=0.025) [81]. Consistent with the open-label study described above [79], synovial volume was not changed by this treatment according to MRI data [81]. Together these studies raise the interesting question as to whether some anti-inflammatory therapies might reduce OA pain through an extra-articular mechanism of action.

TNF and IL-1 inhibitors

TNF and IL-1 are pro-inflammatory cytokines that have been linked to non-neuronal cell-mediated activation of nociceptors (Figure 2) [7]. However, an analgesic benefit of TNF inhibition is not clear [82]. In a clinical trial of 43 patients with erosive and inflammatory hand OA randomised to treatment with the anti-TNF antibody adalimumab (40 mg subcutaneous injections every other week) or placebo for 12 weeks, followed by cross over treatment after washout, no difference was noted in the primary outcome measure of change in hand pain (measured by VAS) at 12 weeks [12]. In another trial of 90 patients with inflammatory hand OA, etanercept (another TNF inhibitor) did not improve pain more than placebo after 24 weeks of treatment [13].

Evidence for the efficacy of IL-1 inhibition in reducing OA pain is similarly unconvincing. The CANTOS study [83], using the IL-1 inhibitor canakinumab to reduce cardiovascular risk in patients with atherosclerotic disease, reported a reduction in the number of 'OA adverse events'. A recent abstract expanding on these findings reported a reduced rate of total joint replacement in the canakinumab-treated group. However, two other experimental studies do not support the notion that IL-1 blockade results in improvement of OA signs and symptoms in OA patients. First, a double-blind placebo-controlled clinical trial of AMG 108 (a monoclonal antibody (mAb) specific for IL-1 receptor type 1,

which blocks both IL-1α and IL-1β) in 223 patients with knee OA showed little, if any, clinical benefit [14]. Second, another randomized double-blind placebo-controlled clinical trial tested ABT-981 (a dual variable domain immunoglobulin targeting both IL-1α and IL-1β) , which also had no therapeutic benefit in 36 patients with knee OA [15].

It is worth noting that current inclusion criteria for these trials requires a patient-reported level of pain and radiographic evidence of OA. Structure-pain relationships are complex and can be confounded by relatively common extra-articular sources of pain such as tenosynovitis and bursitis; therefore, the source of pain for these trial participants might not always be caused by intra-articular OA-related pathology, and measures of synovitis alone might not be sufficient for mechanistic studies. The imaging studies we have discussed [79,81] indicate that the beneficial effect of methotrexate on OA pain might be independent of an effect on synovitis. To clarify this issue, alternate measures of joint inflammation, in addition to MRI, such as expression of inflammatory mediators, are needed to identify whether a particular treatment has an effect on inflammation. This strategy might also help to better define the relationship between inflammation and pain.

With these caveats in mind, the data together suggest that some anti-inflammatory therapies, in particular glucocorticoids (at relatively high concentrations) and methotrexate, might reduce OA pain, but TNF inhibitors and IL-1 inhibitors do not. Furthermore, the MRI data suggest that the beneficial effect of methotrexate on OA pain might be independent of an effect on synovitis.

New approaches to treat OA pain

Peripheral nociceptive pathways

With the exception of cartilage, all of the joint tissues are innervated by nociceptors. Neurotrophins, a family of proteins that play an important role in the regulation of the growth, survival, and

differentiation of neurons in the central and peripheral nervous system, are known to play a critical role in the pathogenesis of chronic pain and afferent sensitization of nociceptors, in conditions such as OA [84]. The neurotrophin family includes NGF, BDNF, neurotrophin-3 (NT-3) and NT-4. Expression of NGF is upregulated in the inflamed synovium and at the osteochondral junction in patients with OA [85,86], with consequent nociceptor sensitisation [16]. Several studies have utilized NGF neutralizing mAbs to reduce OA pain and back pain [87]. Anti-NGF antibody treatment results in substantial analgesic benefits in OA pain, but it also associated with adverse effects, including peripheral neuropathies and rapidly progressive OA [88]. Preclinical work indicates that anti-NGF antibody treatment may have detrimental effects on the integrity of the joint [89], but the mechanism of this effect is not fully understood [27,88,89]. Conceivably, maintaining some neurotrophin function after treatment may be required for cartilage and bone repair to occur in OA; anti-NGF antibodies however ablate NGF signalling as they bind irreversibly to NGF [89].

A bi-specific fusion mAb specific for NGF and TNF (called MEDI7352) is currently in early phase development [90]. NGF binds to tropomyosin-receptor-kinase A (TrKA) and p75 neurotrophin receptors (p75NTR) on sensory neurons, receptors that mediate the effects of neurotrophins (Figure 2b). Thus, blocking TrkA could be an alternative approach to inhibit nociceptor sensitisation by NGF; a study of a specific NGF inhibitor (AR786) in rat models of OA demonstrated prophylactic and therapeutic analgesic benefits [91]. Another potential therapeutic targeting neurotrophins in OA is LEVI-04 (an Fc region of an IgG antibody combined with the neurotrophin receptor p75), which reversibly binds NGF, brain-derived neurotrophic factor, NT-3 and NT-4 and is currently being tested in patients with OA [92] .

The capsaicin receptor transient receptor potential vanilloid subfamily member 1 (TRPV1) is an important integrator of responses to inflammatory mediators and it has a unique expression profile in peripheral nociceptors [93]. As a result of its involvement in nociception, TRPV1 has been a prime target for the development of novel pain reducers. Capsaicin (derived from chilli peppers) interacts

with the TRPV1 channel proteins on nociceptors (Figure 2) to produce initial and specific excitation, then subsequent desensitisation [94]. Topical capsaicin creams are effective and licensed for knee OA and other causes of pain [95]. Also, a phase IIa trial showed substantial reduction in pain on walking for patients with OA three months after two intra-articular doses of highly purified synthetic *trans*-capsaicin (compared with placebo) [96].

GM-CSF

On the basis of preclinical data, successful phase II RA trials targeting either granulocyte macrophage-colony stimulating factor (GM-CSF) or its receptor indicate that GM-CSF has a pivotal function in RA pathogenesis [97]. GM-CSF is a potentially pro-inflammatory cytokine linked to non-neuronal cell-mediated activation of nociceptors (Figure 2a) [7]. After successful and rapid reversal of pain by anti-GM-CSF mAb treatment in the collagenase-induced instability model of OA [98], the anti-GM-CSF antibody GSK3196165 was used in a study of 44 patients with inflammatory hand OA. [99] These patients were randomized to five weekly subcutaneous doses of 180mg GSK3196165 (n=22) or placebo (n=22), followed by three further doses every other week, resulting in consistent trends towards improvement at each time point for all endpoints after active treatment compared to placebo, although intention to treat analysis did not reveal statistical significance for the individual endpoints at week 6. It should also be noted that measured GSK3196165 exposure levels were lower than anticipated from previous studies. The difference in hand pain scores between GSK3196165 and placebo was −0.36 (95% confidence interval [CI] −1.31, 0.58; p=0.442), and increased to −0.89 (−2.06, 0.28; p=0.132) at week 12. The proportion of patients achieving 30% and 50% reductions of average hand pain was higher in the anti-GM-CSF antibody group compared to placebo at each assessment. At week 12, the Australian Canadian Osteoarthritis Hand Index (AUSCAN) pain (0-50) and function (0-90) scores showed a difference (compared to placebo) of -4.7 (-10.1, 0.6; p=0.082) for pain and -8.2 (-19.1, 2.7; p=0.136) for function. Interestingly, dynamic contrast-enhanced MRI did not show any change in synovitis after 12 weeks of treatment [99]. These results need to be confirmed by a larger RCT, but the apparent

discrepancy between improvement in clinical pain scores and unaltered synovitis after active treatment is consistent with methotrexate studies [79,81] and although confirmation is required these data might indicate an alternative mechanism of action, perhaps an effect on cell migration to the spinal cord and DRG [60,61].

GM-CSF–CCL17 pathway - In monocytes and macrophages in vitro and in mouse models of inflammatory arthritis, the transcription factor IRF4 regulates production of the chemokine CCL17 to mediate the pro-inflammatory and algesic (pain causing) functions of GM-CSF [100] (Figure 3). Mechanistically, GM-CSF induces IRF4 expression by enhancing JMJD3 demethylase activity [100] and, by a mechanism still to be elucidated, the regulation of pain by the GM-CSF-CCL17 pathway requires cyclooxygenase 2 activity implying involvement of an eicosanoid(s) such as PGE_2 [100]; this eicosanoid contribution could be CCL17-dependent or -independent. In another study, it was reported that there could be an interdependence of TNF and GM-CSF activities leading to activation of the above pathway which may help explain some of the algesic and pro-inflammatory functions of TNF [101]. Intriguingly, this GM-CSF-CCL17 pathway seems to also regulate collagenase-induced OA pain and disease (that is, in a TNF-independent and IL-1 independent model) [102]. Interestingly, CCL17 mRNA was highly expressed in the bone and cartilage during pain in the rat monosodium iodoacetate OA model [49]. Whether targeting CCL17 could ameliorate pain in patients with OA requires further study, but a first RCT with an anti-CCL17 antibody (GSK3858279) in 98 patients with OA has begun [103].

Central nociceptive pathways

Pain in OA might not only be the result of inflammation and damage in the joint or peripheral sensitization of primary sensory neurons, but could also be driven by changes in the central nervous system (CNS). A central mechanism might explain (in part) the imperfect association between synovitis and OA pain as well as the improvement in OA pain that occurs without a change in synovitis after therapy with methotrexate or anti-GM-CSF antibody, respectively, at least in a subset of patients with

OA. Moreover, pathological changes in the CNS could contribute to the chronic pain ~20% of patients experience after total knee replacement [104,105]. Both sensitization of neurons in the CNS [106] and immune cells seem to be involved in pain [8,107,108]. The role of pain-associated microglia is well established in animal models of chronic pain [109,110], but several studies have shown that leukocytes can also traffic from the peripheral blood into the DRG and spinal cord to actively contribute to nociceptive hypersensitivity [60,61].

Understanding how immune cells and the mediators these cells produce affect chronic pain (reviewed elsewhere [8]) can open up exciting new opportunities to treat pain. For example, strong preclinical evidence shows the involvement of monocytes and macrophages; depletion of these cells improves chronic pain in several pain models, such as hyperalgesia following nerve injury and models of diabetic neuropathic pain [111-113]. Therefore, various therapeutic strategies could be explored to treat pain by targeting migration or activation of monocytes and macrophages, for example by blocking chemokines or their receptors [114], interfering with TLR signalling [110] or inhibiting GM-CSF or its receptor [97]. Whether the improvement in OA pain scores after methotrexate or anti-GM-CSF antibody treatment [81] in the absence of improvement in the synovitis can be partly explained by an effect on monocytes and macrophages in the DRG and spinal cord needs to be explored in future studies.

Conclusions

Joint inflammation, usually monitored as synovitis, is often associated with both OA pain and structural changes but other components of the inflammatory response, such as levels of soluble mediators of inflammation should also be monitored. Therefore, targeting inflammation might limit both disease symptoms and disease progression in a subset of patients with OA. Bi-directional cross-talk between the immune and nervous systems seems to regulate pain, so targeting either or both arms of this cross-talk should broaden the therapeutic options for OA pain. Drugs that target

peripheral nociceptive targets are now in late stage development clinical trials and drugs targeting neurotrophins are proving to be efficacious, but the long-term effects of these drugs on the integrity of the joint need to be understood in relationship to remaining NGF activity after treatment. In addition, interfering with migration and activation of immune cells in the DRG and spinal cord might provide new therapeutic opportunities.

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Author contributions

P.G.C. and P.P.T researched data for the article. All authors contributed to discussions of its content as well as the writing and review or editing of the manuscript before submission.

Competing interests

P.G.C. declares that he has participated in speakers bureaus or is on advisory boards for Abbvie, BMS, Flexion Therapeutics, GSK, Merck Serono, Novartis, Pfizer, Roche and Samumed. J.A.H. declares that he has been a consultant for GSK. P.P.T. declares that he was an employee and

shareholder of GSK, and is presently non-executive director of Levicept. A.D.C. has no competing interests.

Key Points

- OA pain is a huge economic, physical and psychological burden globally
- Inflammation is often associated with OA pain and the development of OA
- Pathological changes in central nociceptive pathways contribute to OA pain
- Bi-directional cross-talk between the immune and nervous systems seems to regulate OA pain
- New therapeutics that target inflammation and the cross talk between the immune and nervous systems are being developed to prevent and treat OA pain

Figure 1. The joint–spine–brain connection in OA nociception.

Anatomy of the basic pain pathway from the periphery to the brain. Noxious stimuli arising, for example, from tissue damage or injury are detected as pain signals by somatosensory neurons (nociceptors) innervating tissues (joint depicted) whose cell bodies are clustered in dorsal root ganglia (DRG). These signals are carried to the dorsal horn of the spinal cord and then transmitted ultimately to the brain via central axonal terminals.

Figure 2. Crosstalk between non-neuronal cells and nociceptive neurons.

a | In response to injury non-neuronal cells (such as immune , mesenchymal, glial and epithelial cells) can release neuromodulatory mediators (such as NGF, PGE_2, and the cytokines, IL-1, TNF and GM-CSF) adjacent to nociceptors to either directly or indirectly increase or reduce pain. Nociceptors in turn can release neuropeptides and neurotransmitters (such as CGRP and Substance P) that modulate the function of the non-neuronal cells. This cross-talk increases the options for alleviating pain. **b** | A zoomed representation of examples of direct interactions of neuromodulatory mediators binding to their specific receptors at the nociceptor terminal, which engages signalling cascades thereby leading to nociceptor sensitization, including decreased activation thresholds for neuronal receptors, for example, TRPV1 and $Na_v1.8$. Released neuropeptides (e.g. CGRP, Substance P) can in turn potentially modulate inflammatory responses.

Figure 3. A GM-CSF–CCL17 axis in inflammatory OA pain and disease [Please see changes to the figure as it is not correct the way it has been drawn].

GM-CSF activates the transcription factor IRF4 in monocytes and macrophages via JMJD3 demethylase to induce production of the chemokine CCL17. CCL17 indirectly results in inflammation and tissue remodelling in arthritic joints and the development of pain by unknown mechanisms, the latter requiring a contribution from an eicosanoid(s) such as prostaglandin E_2; this eicosanoid contribution could be CCL17-dependent or -independent. [98,100,102].

Glossary terms

neurotrophins – a family of proteins that play an important role in the regulation of the growth, survival, and differentiation of neurons in the central and peripheral nervous system

action potentials – the change in electrical potential associated with the passage of an impulse along the membrane of a nerve cell

proalgesic – a mediator which is pain inducing