The challenges of treating osteoarthritis pain and opportunities for novel peripherally directed therapeutic strategies

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Osteoarthritis (OA) is a chronic joint disease that represents an increasingly substantial global burden. Joint pain is the most significant symptom of OA. Unfortunately, current pharmacological treatments for OA pain are often not wholly efficacious, or are associated with serious adverse effects. This lack of effective pain relief has seen the prescription of opioids for OA pain increase over the past decades. The long-term adverse effects of prescribed opioids alongside the increasing prevalence of OA pain highlights the need for alternative analgesics.

Understanding the mechanisms that drive this chronic joint pain is crucial for the development of novel analgesics. OA is a heterogeneous disease, and this is reflected by the diversity of pain phenotypes in people with the disease. Herein, we review current understanding of the biological changes at the joint and within the central nervous system that drive this chronic pain. We particularly focus on the most recent advances in our understanding of the peripheral nociceptive mechanisms that underlie chronic OA pain and highlight how targeting peripheral OA inflammation may open up opportunities for novel analgesics.

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1. Introduction

1.1. Osteoarthritis (OA) and the burden of chronic pain

OA is the most common form of arthritis, estimated to affect 250 million people worldwide, with knee OA having the highest prevalence (Hunter and Bierma-Zeinstra, 2019). OA is also the fastest growing cause of chronic pain worldwide (Collaborators, 2015, 2018), with people experiencing pain symptoms that reflect nociceptive and neuropathic mechanisms. Unfortunately, long-term analgesic options are limited, and as no disease modifying therapies are available, current end-stage disease treatment is reliant on total joint replacement surgery. Although this surgery can be effective, patients often experience long periods of chronic pain before surgery, and this costly treatment may also require revisions later in life. Furthermore, a subset of patients continue to experience pain after surgery, highlighting the need for novel analgesic treatments. This review particularly focuses on the most recent advances in understanding the peripheral nociceptive mechanisms underlying chronic OA pain, highlighting how targeting peripheral OA inflammation may open up opportunities for novel analgesics.

OA is a multifactorial disease, associated with progressive degradation of articular cartilage in single or multiple synovial joints arising from an imbalance in the dynamic equilibrium between the breakdown and repair mechanisms of joint tissues (Dieppe and Lohmander, 2005; Egloff et al., 2012; Felson, 2013), most commonly the knees, generally triggered by wear and tear or trauma. Several joint structures are affected by OA, with cartilage loss (Goldring and Marcu, 2009; Hunter and Bierma-Zeinstra, 2019), synovial inflammation (Dulay et al., 2015), and subchondral bone remodelling evident as the characteristic diagnostic markers (Goldring and Goldring, 2010). The disease manifests first with molecular alterations in joint tissue metabolism, followed by the development of pathogenetic anatomical abnormalities (Kraus et al., 2015). However, the temporal relationship between molecular changes and anatomical abnormalities in joint structure in OA remains...
In the early stages, OA pain is thought to be mechanically-induced, arising from activation and sensitization of pain-sensing (nociceptive) nerve fibres following pathological changes in the affected joint (see Vincent, 2020 for review). OA pain is associated with synovial inflammation and subchondral bone marrow lesions (reviewed in O’Neill and Felson, 2018), but less so radiographic markers of disease progression (Finan et al., 2013). Although treatment with bisphosphonates to target bone marrow lesions has been trialled, meta analyses suggest no significant symptomatic relief or delay in disease progression (Vaysbrot et al., 2018), and recent evidence highlights that this approach does not markedly improve established OA (Ballal et al., 2020). The association of synovial inflammation with OA pain, alongside the remarkable success might benefit people with OA (Robinson et al., 2016). Disappointingly, randomised controlled trials of a range of anti-inflammatory treatments licensed for use in rheumatoid arthritis, including hydroxychloroquine, methotrexate, and TNFα, or IL-1α blocking agents, have revealed limited benefit in human OA (Persson et al., 2018).

Many chronic pain states are underpinned by local sensitization of sensory nerves at the original site of injury and a facilitation of painful (nociceptive) inputs to the central nervous system. These facilitated nociceptive inputs arise as a result of the local generation of pro-nociceptive and inflammatory molecules which collectively sensitise and/or activate sensory nerves (Fig. 1).

The peripheral immune system plays a significant role in the generation of these molecules. Invasion of monocytes into synovium and increases in pro-inflammatory macrophage populations (Miller et al., 2012a; Mondadori et al., 2021; Raghu et al., 2017a), as well as increased osteoclast activity in subchondral bone (Zhu et al., 2019), contribute to OA pain behaviour in rodent models. Multiple classes of molecules are involved in the sensitization of local sensory nerves in OA synovium and/or subchondral bone, including neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), cytokines such as interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNFα), neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P, and protons (see Pattison et al., 2021 for review) (Fig. 1).

Many of these molecules trigger longer-term changes in sensory nerve receptor and channel (including transient receptor potential channel subfamily V member 1; TRPV1 (Julius, 2013) activation, expression, or phosphorylation, leading to longer-term changes in signalling and excitability, driving the development of OA pain (Fernihough et al., 2005). The lowering of thresholds and increased excitability of sensory fibres contributes to aberrant pain sensations, such as hyperalgesia (increased pain) and allodynia (pain in response to non-injurious stimuli), experienced by people suffering from chronic OA pain (Arendt-Nielsen et al., 2010; O’Neill and Felson, 2018). The breadth of changes in nociceptive signalling in multiple joint tissues presents a significant challenge for the treatment of OA pain – targeting a single molecule, pathway or cell type may provide only partial relief, or prove effective in only a subpopulation of patients.

1.2. Peripheral mechanisms of OA pain

In the early stages, OA pain is thought to be mechanically-induced, arising from activation and sensitization of pain-sensing (nociceptive) nerve fibres following pathological changes in the affected joint (see Vincent, 2020 for review). OA pain is associated with synovial inflammation and subchondral bone marrow lesions (reviewed in O’Neill and Felson, 2018), but less so radiographic markers of disease progression (Finan et al., 2013). Although treatment with bisphosphonates to target bone marrow lesions has been trialled, meta analyses suggest no significant symptomatic relief or delay in disease progression (Vaysbrot et al., 2018), and recent evidence highlights that this approach does not markedly improve established OA (Ballal et al., 2020). The association of synovial inflammation with OA pain, alongside the remarkable success might benefit people with OA (Robinson et al., 2016). Disappointingly, randomised controlled trials of a range of anti-inflammatory treatments licensed for use in rheumatoid arthritis, including hydroxychloroquine, methotrexate, and TNFα, or IL-1α blocking agents, have revealed limited benefit in human OA (Persson et al., 2018).

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1.3. Central mechanisms of OA pain

Not all joint damage leads to OA pain, and not all people with OA pain have a lot of damage in the affected joint, supporting the involvement of mechanisms beyond local peripheral pathology, such as dysregulation of peripheral nerves and sensitization of central sensory pathways. Indeed, although total joint replacement provides effective pain-relief in the majority of people, a significant proportion of people still experience persistent chronic pain after surgery (9% of hip replacement and 20% of knee replacement patients (Beswick et al., 2012)), further supporting the presence of central mechanisms. As OA progresses, the experience of pain changes from occurring on movement, to a constant dull ache with unpredictable periods of acute pain (Finan et al., 2013). At this stage, the prolonged increase in peripheral drive from primary afferent fibres innervating the knee joint can lead to sensitization of central pain signalling pathways, identified as a key point of intervention for chronic OA pain.

Fig. 1. Potential Analgesic Targets for Chronic OA Pain. Diagram depicting the major pathogenic changes in OA knee joints (B, right) compared to healthy normal tissue (A, left). Disease progression involves degradation of articular cartilage (blue), and the generation of proinflammatory mediators and growth factors within the joint. This, in turn, leads to inflammation of synovial tissue (synovitis, purple), and altered sensory innervation (red) of joint tissues, including nociceptive innervation of previously aneural articular cartilage (blue), and sensitization of nociceptive primary afferents in multiple tissue layers. Later events include the formation of lesions in the subchondral bone. C: Boxed text indicates potential analgesic targets for OA pain discussed in the present review, based on molecular entities known to be involved in development or resolution of these peripheral pathogenic processes.
pathological process in the development of chronic pain states (Arendt-Nielsen et al., 2018; Hawker et al., 2008). Evidence for central sensitization mediating a proportion of OA pain includes increased temporal summation to repeated painful stimuli, and reduced descending inhibition in some people with OA (Arendt-Nielsen et al., 2010). These processes uncouple pain severity from the degree of peripheral injury, and differing degrees of central sensitization could explain why patients with OA exhibit different pain phenotypes and why patients’ experience of pain does not match the extent of structural changes observed (Arendt-Nielsen et al., 2015). Alongside physiological changes in pain signalling pathways, psychological and affective factors contribute to the extent of OA pain. Chronic OA pain and the attendant loss of mobility and locomotor function can lead to social isolation and psychological distress, including anxiety and depression, both of which are associated with augmented pain severity and increased opioid analgesic intake, with negative consequences for people living with OA. Inadequate pain relief remains the greatest clinical burden in OA, causing significant disability, suffering, and economic impact. For the majority of patients, current treatments focus on exercise and the use of analogues which are not wholly effective and can be associated with serious adverse effects.

2. Current treatments for OA pain

2.1. Acetaminophen and non-steroidal anti-inflammatory drugs

The current frontline analgesic treatments are acetaminophen, and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) (NICE, 2014). Acetaminophen is one of the most commonly used non-prescribed analogues (Duong et al., 2016), however, a systematic review of people with knee and hip OA found that acetaminophen only provides minimal short-term analgesia compared to placebo (Leo-poldino et al., 2019). Non-steroidal anti-inflammatory drugs (NSAIDs) are currently recommended for the frontline pharmacological management of OA pain (Bannuru et al., 2019; Kolasinski et al., 2020). However, there are several safety concerns associated with sustained oral NSAID administration, including hepatotoxicity, risk of renal failure in those with impaired kidney function, increased risk of cardiovascular (CV) events in those with hypertension or other CV disease, and, most importantly, the widely acknowledged negative impacts on the upper gastrointestinal (GI) tract (Scarpignato et al., 2015). These are wide-ranging, from relatively mild dyspepsia and heartburn, to potentially life-threatening complications arising from peptic ulcers, meaning the risks often outweigh the modest analgesia NSAIDs provide (da Costa et al., 2021). Topical administration of NSAIDs is a safer alternative to orally administered NSAIDs, and a systematic review suggests that topical NSAIDs do offer effective pain relief when compared to placebo (Zeng et al., 2018). However, it is still not clear whether these analgesic effects are maintained over long-term use (Zeng et al., 2018). Whilst topical NSAIDs are recommended for the management of knee OA, the distance of the hip joint from the skin may limit their efficacy for hip OA (Kolasinski et al., 2020).

2.2. Use of opioid drugs in OA pain

Despite the overwhelming impact of OA pain, we have been reliant on the same few poorly effective pain medications for decades. Over the last few decades, opioid prescribing for OA pain has become increasingly common, and still remains very high in the UK (Curtis et al., 2019; IBM DataLab U. of O, 2021). Despite NICE guidance (NICE, 2014), only very modest reductions in prescribing are evident since 2016 (Curtis et al., 2019). Indeed, initial prescription of opioids for OA in the UK has significantly increased in the last 5 years (Zeng et al., 2021). In Sweden people with OA are more likely to have incident prescribing of strong opioids (Thorlund et al., 2019), of which over half are reported to be inappropriate according to treatment guidelines (Thorlund et al., 2020).

As waiting times for surgical treatments continue to increase post-pandemic, the numbers of people being prescribed opioids for longer periods of time is also growing (Farrow et al., 2021). Over 62% of people starting strong opioid treatments are female (Jani et al., 2020).

The effects of opioid drugs, like morphine, are mediated by G protein-coupled μ-opioid receptors (MOR), with sites and mechanisms of action widely reviewed elsewhere (see references in Al-Hasani and Bruchas, 2011). MOR, alongside δ and κ opioid receptors, are located in the dorsal horn (DH) of the spinal cord and multiple other pain-responsive brain regions (see references in McMahon et al., 2013) and through their actions at MOR, opioid ligands produce potent, short-duration analgesia. However, repeated and long-term opioid use alters MOR function (see references in McMahon et al., 2013). Long-term opioid use in a mixed population of chronic pain patients was associated with higher metylation of the MOR gene (OPRM1) (Doehring et al., 2013; Viet et al., 2017), which may contribute to loss of opioid-mediated analgesia, appearance of tolerance and the manifestation of opioid-induced hyperalgesia (Colvin et al., 2019). Overall, long-term opioid use is associated with negative outcomes, and there is now a growing evidence base indicating the use of opioid drugs to treat chronic pain states, such as OA.

Clinical studies suggest that prior opioid use can worsen responses to subsequent painful injury. Chronic preoperative opioid use before common elective orthopaedic procedures increased the risk of chronic postoperative opioid use (Broek et al., 2019). A number of factors are associated with prolonged postoperative opioid use following total knee joint replacement (TKR), including age, anxiety, back pain, and preoperative opioid use, leading to the suggestion that weaning of preoperative opioids should be considered (Namba et al., 2018). Comparison of opioid use after TKR in opioid naïve people and people using opioids on the day of surgery reported that a lowered pain report at 6 months was associated with reduced likelihood of continued opioid use, however change in joint pain did not predict opioid use at 6 months (Goelsing et al., 2016). On a longer timescale, joint pain severity, pain catastrophizing, and back pain have been identified as strongly associated with opioid use 4 years following total knee arthroplasty (Valdes et al., 2015).

Experimental studies in rodent models also support the view that opioid use before or during the onset of a chronic pain state can exacerbate the magnitude and the duration of pain responses in models of neuropathic, fracture and post-operative pain (Grace et al., 2016; Li et al., 2019; Loram et al., 2012). Hyperalgesia is mediated by increased neuronal activity and neuroinflammatory signalling, including glial cell activation in the DH and brainstem (see references in McMahon et al., 2013). These events (known as central sensitization) prime DH neurones to future noxious inputs, resulting in persistent increases in neuronal excitability and long-lasting plasticity (Grace et al., 2016). Morphine treatment drives similar neuroinflammatory signalling in the DH (Raghavendra et al., 2002) and brain (Eidson and Murphy, 2013), which may help explain why prior morphine use can increase responses to subsequent painful stimuli.

Overall, the long-term detrimental effects of prescribed opioids, coupled with the increased prevalence of chronic pain, highlight the need for alternative analgesic options to reduce the major health, societal, and economic implications of chronic OA pain. Understanding the mechanisms which underlie the development and maintenance of chronic OA pain is crucial to identify potential new targets for treatment. Rodent models of OA (reviewed in Table 1) have proved valuable tools in this endeavour. Here, we focus on recent advances in understanding of peripheral nociceptive mechanisms which drive joint pain and the opportunities these present for the development of alternative treatments.
Table 1

Some of the most common OA models and their respective pain and pathology phenotypes.

| Model                      | Species | Pain Behaviours | Pathology | Pharmacology |
|----------------------------|---------|-----------------|-----------|--------------|
| **Chemical Induction**     |         |                 |           |              |
| Monosodium iodoacetate (MIA) | Rat     | Dose dependant changes in weight-bearing asymmetry (WB) and paw withdrawal thresholds (PWT) seen from 3 days post-injection (Bove et al., 2006; Sagar et al., 2010). | Dose dependent changes in joint pathology from 7 days post-injection. Severe damage of articular cartilage seen from 14 days (Bove et al., 2003; Ferreira-Gomes et al., 2012). | Morphine reduced mechanical hyperalgesia and allodynia at both the early stage and late stage of the model. Diclofenac and paracetamol reduced mechanical hyperalgesia at 3 days post-injection but was ineffective at later time points (Fernihough et al., 2004). Celecoxib acutely increased mechanical hind-paw withdrawal thresholds at 7 days post-injection. Gabapentin and morphine acutely increased mechanical hind-paw withdrawal thresholds from day 24 post-MIA (Aman et al., 2019). |
|                           | Mouse   | Dose and age dependant changes in both WB from 3 days and PWT from 7 days post-injection (Ogbonna et al., 2015). | MIA-treated knees showed thinning cartilage thickness and proteoglycan loss (Ogbonna et al., 2015). |              |
| **Surgical Induction**     |         |                 |           |              |
| Medial Meniscal Transection (MNX) | Rat     | Changes in WB and PWT seen from 3 days post-surgery (Ashraf et al., 2014; Bove et al., 2006; Huang et al., 2017). With chronic changes in pain behaviours observed up to 35 days. | Early changes in joint pathology observed from 14 days post-surgery, with more severe changes being observed by 21 days (Bendele, 2001). | Indomethacin and dexamethasone attenuated MNX-induced weight-bearing asymmetry (Ashraf et al., 2011). Rofecoxib and Gabapentin acutely reversed weight-bearing asymmetry changes at day 21 post-surgery. Gabapentin also acutely reversed mechanical allodynia at this time point. Celecoxib and morphine reversed weight-bearing asymmetry at 14 weeks post-surgery (Inglis et al., 2008). |
|                           | Mouse   | Early changes in mechanical allodynia observed from 28 days post-surgery (Malnait et al., 2010). Later changes in WB and PWT observed from 12 weeks post-surgery (Gowler et al., 2020; Inglis et al., 2008; McNamee et al., 2010). These pain behaviours are maintained up to 16 weeks post-surgery. | Mild joint damage has been reported from 4 weeks post-surgery, which worsens over time (Bott er et al., 2005; Glasson et al., 2007). Moderate-severe OA-like pathology is seen at 16 weeks post-surgery. |              |
| **Partial Medial MNX**     | Mouse   | Lack of WB asymmetry up to 12 weeks post-surgery. Significant ipsilateral mechanical allodynia and contralateral cold allodynia from 8 weeks post-surgery (Inglis et al., 2008). | Articular cartilage lesions are seen from 4 weeks post-surgery with progression in severity up to 12 weeks post-surgery (Inglis et al., 2008). | Diclofenac reduced post-surgical pain but had no significant effects on pain behaviours at the later time-points. Morphine reversed these changes in pain behaviours at the later time points (Inglis et al., 2008). Meloxicam, indomethacin, and morphine all reduced early joint pain. |
| **Anterior Cruciate Ligament Transection (ACLT)** | Rat     | Increased joint pain as measured by articular incapacitation (Castro et al., 2006) up to 14 days post-surgery (Castro et al., 2006). | Mild chondrocyte loss and articular cartilage fibrillations observed at 7 days post-surgery. Severity of OA-like pathology increased up to 10 weeks post-surgery. |              |
|                           | Mouse   | Significantly increased weight-bearing asymmetry from 3 days post-surgery to 8 weeks post-surgery (Angelby Möller et al., 2020). | Moderate cartilage degeneration and osteophyte formation observed at 8 weeks post-surgery. |              |
| Mechanical Joint Loading   | Mouse   | Lowered PWT and increased WB asymmetry observed at 3 weeks post-loading up to 6 weeks post-loading (3 times per week, for 2 weeks, 9N) (ter Heegde et al., 2020). | Localised articular cartilage lesions observed after 6 loading sessions of 9N over 2 weeks (ter Heegde et al., 2020). Progression of cartilage damage was seen 3 weeks after the 2 week loading period. Orthopaclisis and synovial thickening was seen following the 2 week and 5 week loading period. | Diclofenac and gabapentin reversed mechanical hypersensitivity and weight-bearing asymmetry after 2 weeks of daily dosing (ter Heegde et al., 2020). |
| **Spontaneous Induction**  | Mouse   | No variation in paw withdrawal thresholds, cold sensitivity, or vocalisations in response to knee compression up to 36 weeks of age (Evans et al., 1994). | Progressive severity of OA with age in male mice, with severe joint space narrowing and increased subchondral bone density observed at 11 months of age. Severity of pathology in female mice plateaus at 5 months (Evans et al., 1994). |              |
|                           | Mouse   | At 9 months of age there was a reduction in paw withdrawal thresholds compared to WT controls. There was no alteration in thermal sensitivity at this time point (Allen et al., 2009). | Mild OA-like pathology observed from 3 months of age. At 9 months of age there was a complete loss of articular cartilage observed in Col9a1−/− mice (Hu et al., 2006). |              |
| Col9a1−/−                  | Mouse   | Increased evoked peripheral nerve activity in aged guinea pigs compared to young animals (McDougall et al., 2009). | Mild OA-like pathology seen in some animals at 3 months of age. With the incidence and severity of OA-like pathology progressing with age, with moderate to severe OA observed in guinea pigs 12–18 months of age (Bendele and Hulman, 1988). |              |
| Dunkin Hartley Guinea      | Pig     |                 |           |              |

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3. Potential therapeutic strategies to treat OA pain: Targeting inflammation

Over the past two decades, advances in our knowledge of the changes to the local biochemical environment of the joint have paved the way for the investigation of treatments aimed at reducing these inflammatory processes. In animal models of OA, pain behaviour can be reduced by cyclooxygenase (COX) inhibitors, targeting pain-associated ion channel receptors such as the transient receptor potential cation channel family members ankyrin 1 (TRPA1) (Mollean et al., 2015) and TRPV1 (Kelly et al., 2015; Obeidat et al., 2020), as well as antagonists acting at neuropeptide receptors such as CGRP receptor (Walsh et al., 2015), bradykinin receptor B1 (BKβ1) (Kauffman et al., 2011), and vasodepressant intestinal peptide receptor (VPAC) (McDougall et al., 2006). However, blockade of CGRP via a monoclonal antibody was not effective at treating OA pain in the clinic (Walsh et al., 2015).

3.1. Nerve growth factor (NGF) & OA pain

NGF is the exemplar member of the neurotrophin protein family, and plays a vital role in the development of the peripheral nervous system through supporting neuronal survival (Deppmann et al., 2008). Under normal conditions, articular cartilage is aneural and avascular, however, during OA pathogenesis significant vascularisation and innervation of the articular cartilage occurs (Walsh et al., 2010). Increased NGF expression has been demonstrated at the level of the OA joint, localised to macrophages and fibroblasts within the synovium, and within fibrovascular tissue in the subchondral bone (Walsh et al., 2010). Whether changes in NGF expression in subchondral bone are independent of synovial inflammation remains unclear (Walsh et al., 2010). Several proteins associated with NGF signalling and implicated in nociception are upregulated in articular cartilage in a murine model of OA (Driscoll et al., 2016). A proposed model of OA progression, where cartilage damage leads to activation of inflammatory signalling within chondrocytes (the sole cell type found in healthy articular cartilage) via a process termed ‘mechanoflagellation’ (Vincent, 2019) has been proposed. In this model, mechanoflagellation leads to an upregulation and release of NGF and other pain-induced molecules from chondrocytes following mechanical injury, which promotes neoinnervation of osteochondral junctions (Vincent, 2020, for review).

NGF activates the high-affinity receptor tropomyosin receptor kinase A (TrkA), increasing phosphorylation and activity of TRPV1 channels. After retrograde transportation from the sensory nerve endings in the joint, NGF induces gene expression in the DRG, including pronociceptive neuropeptides substance P and CGRP, and TRPV1 channels. Through these mechanisms, NGF sensitises primary afferent terminals and drives longer-term changes in sensory nerve function, contributing to hyperalgesia. Over the last decade, knowledge of NGF-mediated mechanisms and therapeutic potential has grown, with a few small molecule inhibitors or antibodies developed as potential analgesics (wise et al., 2021; for review). Preclinical studies have shown that anti-NGF monoclonal antibodies attenuate joint pain behaviour in rodent models of both chemically (ishikawa et al., 2015; Xu et al., 2016) and surgically-induced OA (Nwasu et al., 2016), and reduces the number of TRAP positive osteoclasts in subchondral bone (Xu et al., 2016). The potential therapeutic benefits of targeting NGF and blocking its actions at TrkA to reduce chronic pain and improve patients’ quality of life has been widely reviewed (Miller et al., 2017). Two humanized monoclonal anti-NGF antibodies were advanced into phase II and III clinical trials for OA pain; tanezumab (Lane et al., 2016; Sperings et al., 2014), and fasudilumab (Dakin et al., 2019). Although initial reports demonstrated efficacy of intravenous tanezumab on measures of both pain and function in a phase II trial for moderate to severe knee OA (Lane et al., 2010; Schnitzer et al., 2011), adverse effects including increased joint pain, paresthesias, and abnormal peripheral sensitization were also reported by some trial participants. Monitoring of joint pathology following treatment with higher doses of tanezumab alone, or in combination with NSAIDs, revealed an increased incidence of structural changes such as rapid joint space narrowing and chondrolysis, initially identified as osteonecrosis, but later characterised as rapidly progressive OA (RPOA) (Hochberg et al., 2016). These reports lead to suspensions of clinical trials (Hochberg, 2015). Although the pathophysiology of RPOA remains poorly understood, it is thought that the increased incidence in phase II trials of tanezumab could have been partly due to the recruitment of trial participants with advanced OA pathology, including subchondral insufficiency fractures, who were more prone to develop RPOA. Subsequently, trials of lower dose tanezumab without concomitant NSAIDs were able to restart with more thorough pre-trial imaging to exclude participants with existing RPOA, or pathologies likely to predispose to RPOA (Hochberg et al., 2016). Despite these mitigation strategies, however, increased incidence of adverse joint events were also identified in recent trials of lower dose subcutaneous tanezumab alone (Berenbaum et al., 2021; Hochberg et al., 2021). Despite meta analyses suggesting that low doses are effective at relieving hip and knee OA in the majority of patients (Zhao et al., 2022), the persistence of these serious adverse events proved too serious a hurdle for regulatory bodies to accept that the benefits outweigh the risks (Rheumatology, 2021). Pfizer and Eli Lilly recently jointly announced they had ceased development of tanezumab for OA pain (McKenzie, 2021). This failure highlights the challenges of treating pain in heterogeneous diseases such as OA, and underlines the need for greater understanding of the pathogenic mechanisms, as well as subsequent careful stratification of OA patients by pain phenotype to both identify those most likely to benefit from a novel therapy and exclude those potentially at risk. For a comprehensive review, see (Oo and Hunter, 2021).

3.2. Brain-derived neurotrophic factor & OA pain

With the recent concerns about NGF-directed therapies, interest has shifted to alternative neurotrophic targets. Brain-derived neurotrophic factor (BDNF) is vital for neuronal growth and survival (Schwartz et al., 1997). Like NGF, BDNF primarily exerts its effects via a tropomyosin receptor kinase receptor (in this case, TrkB), but also binds to p75NTR. Both BDNF and TrkB are upregulated in the central nervous system in chronic pain states (Michael, 1999; Sarchielli et al., 2007), and people with a hemi-zygous deletion of the Bdnf gene have reduced pain sensitivities (Sapiio et al., 2019), strengthening the link between BDNF and pain. Sequestration of BDNF in the spinal cord reverses pain behaviour responses in neuropathic pain models in both rats and mice (Endo et al., 2009; Yajima et al., 2005). As a result, the mechanisms by which BDNF contributes to central sensitization have been a major focus for the development of potential novel analgesics (see Cappoli et al., 2020 for review). Both BDNF-driven phosphorylation of NMDA receptor subunits and the downregulation of the potassium/chloride co-transporter, KCC2 (slack et al., 2004; Zhang et al., 2008) have been identified as potential mechanisms by which BDNF facilitates nociceptive signalling.

A clinical study reporting a significant positive correlation between plasma concentrations of BDNF and self-reported pain in people with OA (Simão et al., 2014) further supported the investigation of the potential role of BDNF in OA pain. In the OA joint, BDNF and TrkB are localised to nerve fascicles in synovial tissue in OA patients and a murine model of inflammatory arthritis (Grimsholm et al., 2008a, 2008b; Miller et al., 2002). BDNF expression has also been demonstrated in human OA synovial fibroblasts and macrophages (Klein et al., 2012), which release BDNF in response to stimulation of P2X4 receptors by ATP (Klein et al., 2012). Transcriptomic analysis of synovial tissue of patients with high versus low OA pain revealed a pain-associated increase in TrkB mRNA expression (Bratus-Neuenschwander et al., 2018). Building on this literature, we focused on peripheral roles of BDNF in OA pain. We reported the presence of BDNF and TrkB mRNA and protein expression in the synovia of people with knee OA, and a significant positive
correlation between TrkB expression and the expression of the pro-inflammatory chemokine, fractalkine (Gowler et al., 2020). To explore this relationship further, we used experimental models of OA pain in the rat to demonstrate that exogenous administration of BDNF to the knee joint augmented pain behaviour in the monosodium iodoacetate (MIA) model of chemically-induced OA pain, but not in naïve rats. These data indicate altered peripheral sensitivity to BDNF in the OA joint (Gowler et al., 2020). Importantly the sequestration of knee joint BDNF partially reversed established pain behaviours in both in a chemical (MIA) and a surgical (meniscal transection; MNX) model of OA pain. Taken together, our clinical and preclinical data suggest a contribution of the BDNF-TrkB axis to peripheral OA pain mechanisms, supporting further investigation of the therapeutic potential of inhibiting this pathway in OA pain.

3.3. Monocyte chemoattractant protein 1 & OA pain

Alongside the contribution of growth factors to OA pain, attention has turned to other mediators of peripheral inflammation. Monocyte chemoattractant protein 1, also known as CCL2, is a key driver of leukocyte chemotaxis via its high-affinity receptor C-C chemokine receptor type 2 (CCR2) (see Gschwandtner et al., 2019 for review). CCL2 is elevated in both the synovial fluid and synovial fibroblasts of people with OA (Raghu et al., 2017), and serum levels of CCL2 are associated with knee OA severity and progression (Longobardi et al., 2018). In the well-validated murine surgical destabilisation of the medial meniscus (DMM) model of post-traumatic OA, there is also rapid and robust increase in the expression of the gene Ccl2 within the joint (Gschwandtner et al., 2019). The CCL2-CCR2 axis is crucial in the recruitment of inflammatory cells to the joint during the development of OA, however, recent evidence has pushed the potential role of the CCL2-CCR2 axis in inflammatory cells to the joint during the development of OA, however, as it can mediate OA pain to the fore. Data from a clinical cohort has reported a significant positive correlation between patient reported pain scores, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and synovial fluid concentrations of CCL2 (Li and Jiang, 2015).

In the mouse DMM model of post-traumatic OA, CCL2 and CCR2 expression is elevated in the dorsal root ganglia (DRGs) 8 weeks post-surgery and in the synovium 12 weeks post-surgery (Miller et al., 2012b; Raghu et al., 2017). The CCL2-CCR2 pathway is implicated in the recruitment of monocytes to the site of injury, and in line with this observation, a reduction in the numbers of macrophages in both the DRG and the synovium was observed in CCR2−/− mice, when compared to wild type mice following DMM surgery (Miller et al., 2012b; Raghu et al., 2017). Interestingly, there was a delay in the onset of pain-related weight bearing changes when CCL2−/− and CCR2−/− mice underwent DMM surgery, compared to wild type mice (Miota Zarebska et al., 2017). Administration of a CCR2 specific antagonist over the first 4 weeks post-DMM surgery reduced weight-bearing asymmetry, cartilage damage, and subchondral bone damage at the 8 week time-point (Longobardi et al., 2017). More recently, the receptor CCR2 has been localised to GRP-positive afferents in the knee joint of mice following DMM surgery (Ishihara et al., 2021), and injection of CCL2 into the knee joint evoked excitatory responses in these sensory afferents. These preclinical data suggest that the CCL2-CCR2 axis may have both direct effects on sensory nerves as well as indirect effects via neuro-immune interactions, and therefore disrupting CCL2-CCR2 signalling may have analgesic potential in OA.

3.4. The resolution of inflammation: implications for pain mechanisms

Acute inflammation and pain following injury have essential protective roles to ensure healing. However, the chronic inflammatory processes that occur with ongoing joint degradation in OA are mal-adaptive and contribute to the development of chronic OA pain. Key mediators regulating the inflammatory response are the bioactive lipids derived from the polyunsaturated fatty acids (PUFAs). The omega-3 fatty acid α-linoleic acid and omega-6 fatty acid linoleic acid are essential fatty acids and are obtained from dietary sources (Saini and Keum, 2018). These essential fatty acids are elongated and saturated to form eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) from α-linoleic acid and arachidonic acid (AA) from linoleic acid (Wiktorow ska-Owezarek et al., 2015). These three fatty acids are the precursors for a wide range of mediators which are generated by three main enzymatic pathways: the cyclooxygenases (COX), the lipoxygenases (LOX), and lastly the cytochrome P450s (CYP450) (Needleman et al., 1986). The lipid mediators derived from AA, EPA, and DHA play an active role in the initiation, maintenance, and resolution of inflammation (Gilroy and Bishop-Bailey, 2019, for review).

The return to normal tissue homeostasis is an active programmed response involving the local generation of endogenous specialised pro-resolution molecules (SPMs) (Buckley et al., 2014). The major SPMs identified to date are D and E series resolvins (RvD and RvE), maresins, and protectins. These are produced from omega-3 fatty acids via cyclooxygenase-2, cytochrome P450, and lipoxygenase pathways by multiple cell types, including monocytes/macrophages. SPMs have local effects to shut-down inflammatory signalling in cells and in vivo via multiple mechanisms, including blockade of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, suppression of cytokine and chemokine production, stimulation of macrophage phagocytosis, and regulation of leukocyte trafficking and clearance (Buckley et al., 2014). Failure to mount a resolution response is thought to contribute to ongoing pathogenesis in many classical and non-classical inflammatory diseases, including stroke, cardiac disease and OA (Chiang and Serhan, 2020).

Whilst the SPMs display potent anti-inflammatory and anti-nociceptive properties, they are rapidly metabolised in vivo, limiting their analgesic potential. One strategy to overcome this hurdle is the development of metabolically-stable molecules with similar biological activities to the SPMs. A stable mimetic of RvD1 reduced leukocyte infiltration and increasing macrophage phagocytosis (Orr et al., 2015), whether this mimetic shares the anti-nociceptive properties of RvD1 remains to be determined. The D series resolvins precursor, 17-hydroxydocosahexaenoic acid (17-HDHA) has greater stability in vivo, and 17-HDHA treatment has been shown to increase concentrations of all D series resolvins (Buckley et al., 2014). There is a natural variability in circulating levels of 17-HDHA in the general population, and lower levels of 17-HDHA are associated with higher pain scores in healthy volunteers and in people with OA (Valdes et al., 2017). Levels of an E series resolvins in synovial fluid were also negatively correlated with arthritis pain (Barden et al., 2016). The link between 17-HDHA and pain was strengthened by our demonstration that systemic 17-HDHA has robust inhibitory effects on pain responses in rodent models of OA pain (Huang et al., 2017), with others showing similar effects in inflammatory arthritis (Lima-Garcia et al., 2011). Spinal administration of the resolin RvD1 in an established mode of OA pain produced only a modest inhibition of evoked response of spinal neurones to noxious stimuli (Meesawatsom et al., 2016), possibly suggesting a predominant peripheral site of action. RvD1 suppresses the expression of the pro-inflammatory mediators MMP13 and IL-1B in human OA fibroblast-like-synoviocytes (Su et al., 2022), supporting a possible peripheral site of action in the injured joint.

Alongside their role in curtailing the inflammatory response leading to Alleviation, in pain, the resolvins may have more direct anti-nociceptive properties. RvD1 and RvD2 are analgesic in models of inflammatory and neuropathic pain (Luo et al., 2019), driving a cascade of inhibitory effects on TRPV1, TRPA1 activity, NMDA receptor activity and TNF-α expression (Rob et al., 2020). The SPM maresin 1 also has direct effects upon sensory nerve cell body activity and neurotransmitter release (Hwang et al., 2019), whilst protectin D1 (PD1) prevents TNF-α and TRPV1 mediated spinal cord synaptic plasticity (Park et al., 2011).

Whilst these data are promising, lipid signalling is highly complex,
with multiple intersecting synthetic and metabolic pathways involving an array of bioactive molecules, with wide scope for compensatory regulation if one aspect of the pathway is disturbed. Furthering our understanding of the in vivo functions of resolvins and associated bioactive lipids will enable development of therapeutic tools to augment their in vivo activities, and could lead to the development of novel effective analgesics for the treatment of chronic pain conditions such as OA. Targeting the receptors which mediate the activities of the SPMs may also be of significant clinical interest. A recent review paper describes the current strategies being used to target these receptors to modulate the inflammatory response (Park et al., 2020). These same strategies may also have important implications for the development of novel analogesics.

3.5. Targeting soluble epoxide hydrolase in OA pain

The epoxyeicosatrienoic acids (EETs) are derived from arachidonic acid (AA) following oxidation via the CYP450 pathway (Roman, 2002; Zeldin, 2001), and are of increasing interest due to their anti-inflammatory and anti-nociceptive effects. EETs are also short-lived in vivo, being rapidly hydrolysed by the enzyme soluble epoxide hydrolase (sEH) into their respective diols (Chacox et al., 1983). Like the SPMs, the EETs have significant anti-inflammatory effects (Bystrom et al., 2011, 2013; Fleming, 2007), mediated by inhibition of NF-κB nuclear translocation, thereby inhibiting the downstream production of pro-inflammatory cytokines (Node et al., 1999). Intra-plantar administration of the EETs acutely reverses carrageenan-induced pain behaviour in rats (Morisseau et al., 2010) and topical administration of the EETs proforallically reduced pain behaviour in rat models of inflammatory pain (Inceoglu et al., 2006). These data suggest that the EETs may act as anti-hyperalgesic molecules through peripheral mechanisms. It is important to note that in vitro data suggests that high concentrations of 8,9-EET can induce calcium influx in a small subset of DRG neurons (Brennies et al., 2011).

Recent evidence indicates that this lipid pathway may be an exciting target for the treatment of OA pain. We have previously shown that levels of some of the EET metabolites, DHETs, in synovial fluid are positively associated with both OA severity and progression in individuals with OA (Valdes et al., 2018). In line with this observation, inhibition of sEH to stabilise endogenous EET levels reduced pain behaviours in a model of spontaneous canine OA pain (Gower et al., 2021). Building upon these data, we have reported that single nucleotide polymorphisms of the sEH gene (EPHX2) and plasma levels of the EETs and DHETs are associated with pain measures in people with chronic OA (Gower et al., 2021). These data suggest there is a perturbation of this enzymatic pathway in people with chronic OA, which may contribute to joint pain. To investigate this further, we demonstrated that both chronic and acute administration of a sEH inhibitor robustly reversed established OA pain behaviour and reduced circulating concentrations of the DHETs in the well-established DMM model of OA pain (Gower et al., 2021). The down-stream mechanism(s) through which sEH inhibitors produce analgesia remain to be fully elucidated. The EETs have been shown to interact with peroxisome proliferator-activated receptor gamma (PPARγ) (Liu et al., 2005; Samokhvalov et al., 2014), which is known to reduce inflammatory and neuropathic pain responses (Maeda and Kishioka, 2009), and PPARγ-regulated transcription is key in reducing microglial activation and oxidative stress (Bernardo and Minnelli, 2007; Khababova et al., 2019; Mansouri et al., 2017; Morgenweck et al., 2010, 2013). There is evidence that the EETs modulate pro-inflammatory lipids, as levels of both PGD2 and PGE2 in inflammatory pain states are reduced (Inceoglu et al., 2006; Wagner et al., 2013) and sEH inhibition reduces inflammation-induced increases in spinal levels of COX2 mRNA (Inceoglu et al., 2008). However, sEH inhibitors can reverse pain behaviour induced by direct administration of PGE2, suggesting that the effects of sEH inhibitors are not exclusively via effects on COX2 expression (Inceoglu et al., 2011). sEH inhibitors also modulate the expression of the LOX metabolites the HODEs and the HETEs, which may play an important role in their analgesic effects (Schmelzer et al., 2005). Modulation of the epoxy fatty acid pathways appear to have robust pre-clinical analgesic efficacy, and may represent an exciting therapeutic target for clinical OA pain. However, more work is still needed to fully understand the mechanisms underlying the anti-nociceptive properties of the EETs. There is also the question of whether the DHETs are just non-active end-products of this enzymatic pathway, or if they have their own pre-nociceptive activities.

4. Conclusions

OA pain still represents a major clinical and societal burden. New understanding about the mechanisms underlying OA pain provide hope for the future development of effective therapeutics. However, OA pain is complex and multi-faceted, being mediated at all levels of the pain neuraxis with variability in both the peripheral drivers and degree of central sensitization producing different subjective experiences of pain (Gwilym et al., 2009). In this review, we have focussed on the contribution of peripheral inflammation at the site of the joint to OA pain, and the resultant search for novel analgesic targets. Blocking the early pathogenic changes in the injured joint has the potential to prevent the development of peripheral sensitization, and thereby the transition from acute to chronic OA pain, however this does require early diagnosis of OA, and identification of which peripheral mechanisms are at play. OA impacts upon all tissues within the joint, and the relative contributions of synovitis, abnormal subchondral bone remodelling, and neo-innervation of the cartilage to the resultant pain phenotype are still not fully understood. Phenotyping patients based on the principle peripheral driver of their pain may allow for targeted therapeutic strategies which could provide more effective analgesia.

References

Al-Hassani, R., Bruchas, M.R., 2011. Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology 115, 1363–1381. https://doi.org/10.1097/ALN.0b013e31821bb36f.
Allen, K.D., Griffith, T.M., Rodriguez, R.M., Wetsel, W.C., Kraus, V.B., Huebner, J.L., Boyd, L.M., Setton, L.A., 2009. Decreased physical function and increased pain sensitivity in mice deficient for type I collagen. Arthritis Rheum. 60, 2684–2693. https://doi.org/10.1002/art.24783.
Amay, Y., Pitcher, T., Ballard, C., Malcangio, M., 2019. Impaired chronic pain-like behaviour and altered epidergic system in the TASTPM mouse model of Alzheimer’s disease. Eur. J. Pain 23, 91–106. https://doi.org/10.1016/j.ejpain.2018.
Angeby M. Möller, K., Aulin, C., Babarapo, A., Svensson, C.I., 2020. Pain behaviour assessments by gait and weight bearing in surgically induced osteoarthritis and inflammatory arthritis. Physiol. Behav. 225, 113079. https://doi.org/10.1016/j.physbeh.2020.113079.
Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H., Graven-Nielsen, T., 2010. Sensitization in patients with painful knee osteoarthritis. Pain 149, 573–581. https://doi.org/10.1016/j.pain.2010.04.003.
Arendt-Nielsen, L., Skov, S.T., Nielsen, T.A., Petersen, K.K., 2015. Altered central sensitization and pain modulation in the CNS in chronic joint pain. Curr. Osteoporos. Rep. 13, 225–234. https://doi.org/10.1007/s11914-015-0275-x.
Arendt-Nielsen, L., Morlion, B., Perrot, S., Dahan, A., Dickenson, A., Kress, H.G., Wells, C., Bouhassira, D., Drewes, A.M., 2018. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur. J. Pain 22, 216–241. https://doi.org/10.1016/j.ejpain.2018.
Ashraf, S., Mapp, P.F., Burston, J., Bennett, A.J., Chapman, V., Walsh, D.A., 2014. Augmented pain behavioural responses to intra-articular injection of nerve growth factor in two animal models of osteoarthritis. Ann. Rheum. Dis. 73, 1710–1718. https://doi.org/10.1136/annrheumdis-2013-204316.
Ashraf, S., Mapp, P.F., Walsh, D.A., 2011. Contributions of angiogenesis to inflammation, joint damage, and pain in a rat model of osteoarthritis. Arthritis Rheum. 63, 2700–2710. https://doi.org/10.1002/art.30422.
Ballal, P., Sury, M., Lu, N., Duryea, J., Zhang, Y., Ratzlaff, C., Neogi, T., 2020. The role of oral bisphosphonates to bone marrow lesion volume among women with osteoarthritis. Osteoarthritis Cartilage 28, 1325–1329. https://doi.org/10.1016/j.
joca.2020.07.006.
Bannuru, R.R., Osani, M.C., Vaysbrot, E.E., Arden, N.K., Bennett, K., Bierna-Zeinstra, S.M.A., Kraus, V.B., Lohmander, L.S., Abbott, J.H., Bhandari, M., Blanco, F.J., Espinosa, R., Haugen, J.K., Lin, J., Mandi, L.A., Meulen, E., Nakamura, N., Snyder-Mackler, L., Trojan, T., Underwood, M., McAlindon, T.E., 2019. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 27, 1578–1589. https://doi.org/10.1016/j.joca.2019.06.011.
chronic osteoarthritis joint pain. Pain 161, 61–73. https://doi.org/10.1097/j.
pain.0000000000001131.
Gower, Peter R.W., Mapp, P.I., Burston, J.J., Shihab, M., Walsh, D.A., Chapman, V.,
2009. Expression patterns of neurotrophins and neurotrophin receptors in articular chondrocytes and inflammatory infiltrates in knee joint arthritis. Cells Tissues Organs 188, 299–309. https://doi.org/10.1159/000121432.
Grimhols, O., Rantapää-Dahlqvist, S., Iläinen, T., Forsgren, S., 2008b. Blockade of
BDNF in RA is downregulated in plasma following anti-TNF treatment but no correlation with inflammatory parameters. Clin. Rheumatol. 27, 1289–1297. https://doi.org/10.1007/s10067-008-9194-1.
Guschwander, M., Deurer, M., Hildes, K.S. 2010. More than just attractive: how CCL2
associated with experimental osteoarthritis in mice. Arthritis Res. Ther. 23, 103. doi.org/10.1002/art.23870.
Hawker, G.A., Stewart, L., French, M.R., Cibere, J., Jordan, J.M., March, L., Suarez-
Gwilym, S.E., Keltner, J.R., Warnaby, C.E., Carr, A.J., Chizh, B., Chessell, I., Tracey, I.,
Gschwandtner, M., Derler, R., Midwood, K.S., 2019. More than just attractive: how CCL2
925–929. https://doi.org/10.1073/pnas.1101073108.
Lane, N.E., Schnitzer, T.J., Birbara, C.A., Mokhtarani, M., Shelton, D.L., Smith, M.D.,
Brown, R.M., Egan, G.T., 2010. Tanezumab for the treatment of pain from osteoarthritis of the knee. N. Engl. J. Med. 363, 1521–1531. https://doi.org/10.1056/NEJMoa0910150.
Leopoldino, A.O., Machado, G.C., Ferreira, P.H., Pinheiro, M.B., Day, R., McLachlan, A. J., Hunter, D.J., Ferreira, M.L., 2019. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD012373. 2019.
Lü, L., Jiang, B.-E., 2015. Serum and synovial fluid chemokine ligand 2/monocyte
chemoattractant protein 1 concentrations correlate with symptomatic severity in patients with knee osteoarthritis. Ann. Clin. Biochem. 52, 276–282. https://10.1177/0000000000001488.
Klein, K., Aeschliman, A., Jordan, S., Gay, R., Gay, S., Sprott, H., 2012. ATD induced
brain-derived neurotrophic factor expression and release from osteoarthritic human fibroblasts is mediated by purinergic receptor P2X4. PLoS One 7. 10.1371.
journal.pone.0036693.
Kolasinski, S.L., Neogi, T., Hochberg, M.C., Oatis, C., Guyatt, G., Block, J., Callahan, L.,
Cohenhaver, C., Dodge, C., Felson, D., Gellar, K., Harvey, W.F., Hawker, G., Herzig, E., Kwoh, C.K., Nelson, E.A., Samuel, J., Scanzello, C., White, D., Wise, B.,
Altman, R.D., DiRenzo, D., Fontanarosa, J., Girardi, G., Ishimori, M., Misra, D.,
Shah, A.A., Stumagel, A.K., Thoma, L.M., Turgonbaev, M., Turner, A.S., Reston, J.,
Anderson, N.D., Cheng, K., Greene, L.I., Berkelhammer, D., Zhang, Y., Ellis, A.L.,
Cheng, K., Greene, L.I., Berkelhammer, D., Zhang, Y., Ellis, A.L., Brown, M.T., West,
C.R., Verburg, K.M., Garber, M., Gordon, R.K., 2008. Understanding the pain experience in hip and knee osteoarthritis - an OARSI/OMERACT initiative. Osteoarthritis Cartilage 16, 415–422. https://doi.org/10.1016/j.ostcar.2007.12.017.
Hochberg, M.C., Carrino, J.A., Schnitzer, T.J., Guermazi, A., Walsh, D.A., White, A.,
Olsen, S., Fountaine, R.I., Hickman, F., Faxon, G., Viktrup, L., Brown, M.T.,
Liu, Y., Zhang, Y., Schmelzer, K., Lee, T.S., Fang, X., Zhu, Y., Spector, A.A., Gill, S.,
Paton, K., Huang, J., Wong, A., McWilliams, D.F., Okine, B.N., Barrett, D.A.,
Gowler, Peter R.W., Mapp, P.I., Burston, J.J., Shahtaheri, M., Walsh, D.A., Chapman, V.,
Gowland, O., Tocchetti, C.G., 2016. The role of maresins in joint edema and lesion in a rat model of osteoarthritis. Osteoarthritis Cartilage 23, 2023–2029. https://doi.org/10.1016/j.ostcar.2016.07.031.
