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Modelling Pathology:Pain Relationships in Osteoarthritis

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Osteoarthritis (OA) results from joint pathology that is clinically associated with pain. It may be the shared end result of various initiating factors, including trauma or immune mediated inflammation. Historically, OA has been labeled as a “non-inflammatory arthritis” or as a “wear and tear disease”. From a pathogenesis standpoint, these labels represent half-truths. Inflammatory mediators play a critical role in pathologic processes across the joint, even though inflammation might be less pronounced in OA than in rheumatoid arthritis. Aberrant joint mechanics and altered chondrocyte mechanotransduction also play roles in the progression of OA. However, increased joint use does not necessarily mean more joint damage or pain. Indeed, rehabilitative techniques can be effective for both cartilage preservation and symptom improvement. The breadth of initiating factors and pathological changes in OA populations has raised the idea that OA is an umbrella diagnosis covering multiple phenotypes.

OA pain mechanisms and experience are similarly diverse across OA populations. Pain may be intermittent or constant, triggered by biomechanical factors or at rest. It may be associated with stiffness, or with neuropathic characteristics such as burning sensations. It may be localized, or diffuse or widespread suggesting central nervous system sensitization. OA pain is often only weakly associated with joint structural change, and the diversity of pathological phenotypes can help to explain this noted discordance[2, 3]. Bone marrow lesions and synovitis help to explain part of the discordance between symptoms and the changes seen with plain radiographs[4, 5]. Even so, the broad spectrum of OA pain cannot easily be explained by joint structure alone.

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Preclinical models, where the initiation of OA is known and controlled, should be a powerful tool for identifying mechanistic links between OA pathogenesis and symptomology. Several models previously have been described, variously initiated by chemical, surgical or inflammatory insults, each resulting in osteochondral pathology, osteophytosis and pain behavior that resemble those in human OA. Each model might, more or less, reflect subpopulations of people with OA, and therefore differences between animal models have potential to help unravel the complex pathology:pain relationship seen in humans. Furthermore, longitudinal assessment of animal models can reveal changing pathology:pain relationships over time. The work in this issue by Zaki, Smith, and Little seeks to determine whether behavioral characteristics of pain and transcriptional changes in the dorsal root ganglia (DRG) are phenotype-specific using both a traumatically-induced OA model (destabilized medial meniscus, DMM) and an immune-mediated inflammatory model (antigen-induced-arthritis, AIA), each of which demonstrated pathological changes of OA from as early as 4 to 8 weeks. Strengths of this work include the use of multiple behavioral assays to characterize the pain response of the animal, including evaluation of tactile allodynia, thermal hyperalgesia, mechanical hyperalgesia, weight-bearing, and stride length. Moreover, behavioral characterizations were coupled to evaluations of transcriptional changes in the innervating DRG.

The team identified distinct behavioral profiles between the two models. During the acute phase, the AIA model showed heightened tactile allodynia, mechanical hyperalgesia, and asymmetric weight distribution relative to the DMM model, and during late-stage OA, the DMM model showed increased mechanical hyperalgesia relative to the AIA model. These distinctions in animal behavior were related to unique transcriptomic changes in the innervating DRG. AIA transcriptional changes in the DRG resolved by late-stage OA, whereas DMM-operated animals had elevated DRG transcript levels of *Calca, Trpa1, Trpv1, and Trpv4* in late-stage OA. Moreover, transcriptional changes showed moderate correlations to behavioral shifts in the animal, which were on par or stronger than correlations between joint level histopathology and behaviors. Thus, as stated with the article's title, the data from Zaki, Smith, and Little importantly support the idea that there might be unique pathology:pain relationships that relate to what you measure (what behavior), when you measure it (what disease stage), and how you got there (what etiology).

While the work by Zaki, Smith and Little represents a comprehensive evaluation of these relationships in two OA models, even their findings might underestimate the complexity of OA pain. For example, OA pathology and pain can importantly differ between males and females. Recently, O'Brien and McDougall[6] demonstrated the joint nociceptors of male and female rats undergo different neurophysiologic remodeling after a medial meniscus transection (MMT) surgery, which might relate to sex differences in tactile allodynia and asymmetric weight bearing. Differences in behavioral profiles between OA models have been repeatedly noted[7], and even when behavioral profiles are similar, joint damage might not be. For example, gait abnormalities developed similarly in rats with medial collateral ligament transection (MCLT) and MCLT+MMT despite marked differences in cartilage damage[8]. Furthermore, a standardized insult such as medial meniscal transection can result in very different pain outcomes depending on genetic or psychological context, despite similar pathological change in the joint[9]. Whereas the common mantra in medicine is to

treat the underlying pathology rather than the symptoms, OA pathology is multifaceted and the pathologic factors driving OA symptoms can vary across the disease stage and with a myriad of other factors. Through additional comprehensive studies (like the study conducted by Zaki, Smith, and Little) which include OA symptoms, joint pathology, and evaluation of neural mechanisms, these pathology-pain relationships will continue to take form, helping to identify key symptom-driving features for specific OA stages, etiologies, and phenotypes.

A key message from the work of Zaki, Smith, and Little is that what you see depends on what you measure. They show that different pain behaviours in mice map to different models, pathologies and timecourses. Pain is not a single entity, and therefore cannot be adequately captured by a single outcome measure. Furthermore, different outcomes map to different pain mechanisms. In humans, weight-bearing rather than non-weightbearing pain severity was specifically associated with localized bone marrow lesions[10]. In rodents with knee OA, paw withdrawal thresholds reflect central sensitization. The most appropriate outcome measure must be selected for the hypothesis to be tested, whether mechanistic or patient-centered. For exploratory analyses, multiple pain-related outcomes are needed. It might be expected that different pain-related outcome measures should correlate with each other, as also structural elements of OA such as joint space narrowing, osteophytosis and synovitis are typically inter-correlated. However, mechanistic components of pain might be sufficiently discrete that such correlation can be weak or absent, as found by Zaki, Smith, and Little.

Even as we begin to create a better picture of pain-pathology relationships in OA, it is important to recognize that OA pain involves physiologic systems far beyond the joint. The work by Zaki, Smith, and Little demonstrate how OA, at different disease stages, can alter nociceptive fields surrounding the joint and transcriptional profiles in the innervating DRGs. Increased nociceptive drive from the OA joint could lower activation thresholds in dorsal horn neurons of the spinal cord[11]. Chronic OA pain is associated with changes in brain connectivity and descending modulation of nociceptive pathways. These functional changes have been labelled ‘nociplastic pain’, to distinguish them from direct effects of joint tissue or nerve injury[1, 12]. Nociplasticity may be a consequence of persistent nociceptive activity, but might also result from chemicals such as nerve growth factor produced by the osteoarthritic joint, or from systemic or even psychological factors. Evidence of central sensitization increases with time after OA induction or symptom onset, both in rodents and in humans, and nociplasticity may contribute to the chronification of OA pain. However, further research is needed to elucidate whether these patterns differ between unique OA etiologies, and what pathological factors in the joint contribute to this nociplasticity. Finally, changes to peripheral signals are ultimately interpreted by the brain. Here, social, psychological, and environmental stressors can combine to affect a patient’s interpretation of pain and an animal’s behavioral response.

In an important percentage of people with OA, current analgesic agents such as non-steroidal anti-inflammatory drugs can become inadequate for pain control[13]. A loss of response to anti-inflammatory drugs and increasing dependence on opiate analgesics has been associated with symptoms more commonly associated with neuropathic pain, and possibly indicative of substantial nociplasticity. In OA animal models, histopathological

evidence of neuronal remodeling has also been reported in the form of truncated nerve endings around the OA joint[14] and evidence of neurovascular invasion at the bone-cartilage interface[15]. Here, again, while changes in innervation patterns have been reported, differences across OA etiologies, animal sex, and OA disease stage are often incompletely documented.

We have reached the nascent stages of understanding pathology:pain relationships in the context of osteoarthritis. Many factors still need to be investigated more thoroughly, including sex effects, immune contributions, neural changes surrounding and beyond the joint, and the impacts of age and disease duration, to name but a few. However, as we begin to further decipher the complex pathology:pain relationships in OA, we open the possibility of pinpointing new biomarkers that move us further towards personalized medicine, identifying unique OA phenotypes, and modeling them so that they can be targeted with specific therapeutics.

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