Why we should study pain in animal models of rheumatic diseases

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Pain is a key symptom in rheumatic and musculoskeletal diseases. Its management relies on standard pharmacological (acetaminophen, non-steroidal anti-inflammatory drugs, opiates, centrally acting drugs) and non-pharmacological (physiotherapy, cognitive behavioural therapy) interventions. For many patients, however, these treatments do not provide adequate pain relief, and the chronic use of analgesic drugs is associated with considerable toxicities. As discussed by Borenstein *et al.* in this Supplement, the rheumatology community has a responsibility to elucidate pain pathways in rheumatic disorders, with the eventual goal of developing more efficacious and safer therapies.

The International Association for the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". While this definition implies that pain has strong emotional and cognitive components, in its very essence pain is a sensation that is triggered when the nervous system detects and interprets a variety of (potentially) noxious stimuli. These harmful stimuli may be mechanical, chemical, or thermal in nature, and are detected by specialised sensory neurons that innervate peripheral tissues, including joints (reviewed in Woller *et al.* in this issue).

From a neurobiological perspective, pain can be classified into four broad categories (1). First, nociceptive pain detects potentially damaging stimuli (for example, when we touch a sharp or very hot object) and serves as an alarm that triggers a withdrawal reflex and autonomous reactions. Secondly, in inflammatory pain, sensitivity of the nervous system is heightened due to the action of sensitising factors such as pro-inflammatory cytokines or products generated by tissue injury (2). As a result, stimuli that normally should not cause pain now do, a phenomenon that is termed "allodynia". Inflammatory pain serves a protective function; for example, we avoid putting weight on an injured limb to stop it from hurting, and this behaviour prevents further damage and promotes repair. Hence, nociceptive and inflammatory pain are essential for the well-being of the organism, even though inflammatory pain can occur as part of a pathological process such as rheumatoid arthritis (RA). In contrast, pathological pain, which results from abnormal functioning of the nervous system, is not protective, but maladaptive (1): neuropathic pain results from damage to the nervous system, but there are also painful conditions in which there is no obvious damage or inflammation, often referred to as dysfunctional pain (such as pain in fibromyalgia).

Rheumatology is concerned primarily with chronic pain that can have elements of all these categories – nociception, inflammation, neuropathy, dysfunctional pain. Chronic pain can be heterogeneous based on its location, precipitating factors or responsiveness to analgesics and it can have different qualities such as "intermittent", "constant", "dull", "burning", or "stabbing". Chronic pain is not just acute pain that keeps on going, but it is initiated and maintained by multiple mechanisms, including peripheral sensitisation, central sensitisation, decreased descending inhibition, and structural plasticity in peripheral and central neuronal circuits (3-5). While there is definitely overlap in clinical presentation and susceptibility to pharmacological modulation, mounting evidence suggests that pain associated with different chronic diseases of distinct aetiology can involve distinct contributing mechanisms (6).

Rheumatic diseases are driven by very diverse pathogenic pathways, with var-

ying contributions of inflammation, the immune system, tissue destruction, and tissue remodeling, such as the remodeling of the bone that occurs as part of osteoarthritis (OA) or spondyloarthritis (SpA). It is, however, an unanswered question whether or not the pathogenic mechanisms of pain in these diseases differ. This should be considered an important question in our field, because elucidating specific pain mechanisms associated with specific rheumatic diseases is likely to facilitate the development of targeted analgesic therapies.

To tackle this challenge, disease-specific animal models may offer great value. It is a reasonable expectation that detailed studies in preclinical models of rheumatic diseases will aid in guiding and complementing the clinical research that is discussed in this supplement. Preclinical pain research traditionally has focused on eliciting a specific type of pain by certain targeted injuries. For instance, zymosan injected into the hindpaw triggers acute inflammatory pain, while neuropathic pain can be induced by ligating the lumbar 5 spinal nerve (known as the Chung model) (7). However, these approaches model pain states, not diseases.

Joint pain has been modeled by intra-articular injection of irritants such as carrageenan, inducing acute inflammation associated with pain behaviours such as hyperalgesia (8, 9). Again, such approaches induce inflammation and hence pain, and are therefore highly useful for elucidating basic pain pathways. However, they do not inform us about the role that these pathways play in specific diseases. As a whole, our research community does not have a tradition of studying pain associated with the most common rheumatic diseases in animal models. A PubMed literature search performed on September 5, 2017 revealed the following numbers: "animal models of osteoarthritis", 2863 papers; adding the word "pain" reduced it to 470 papers (16.4%). The same search for RA revealed 6284 papers, 267 with pain (4.2%) and for SpA 282 papers, just 8 of which included some form of pain assessment (2.8%). This seems at odds with the importance of the clinical problem of pain associated with these diseases (see Clauw *et al*., Walsh *et al*., Kiltz *et al*. in this supplement, and (10)), irrespective of whether disease-modifying treatments exist (as for RA) or not (as for OA).

Over the past decade, frustration with the poignant discordance between the boom in basic understanding of pain mechanisms (mostly based on animal model research) and the absence of translating these discoveries into clinically efficacious and safe new treatments, has led many to question the value of animal models – a sentiment not limited to pain research (11, 12). As a result, there has been strong emphasis in the field on improving *in vivo* modelling of pain, by improving the choice of the models, the subjects (*e.g*., paying attention to sex and age of the animal), the pain assays, standardisation, and so on. In rheumatology, this has transpired in the area of OA, where research is increasingly incorporating the study of pain and its mechanisms as an integral part of the disease in animals (see McDougall *et al*. in this supplement, and reviewed in (13)), likely reflecting the enormous unmet medical need in this common disease for which no disease-modifying treatments currently exist (10).

Major lessons are emerging from these approaches. For example, studies using different models to induce OA in laboratory animals suggest that different types of OA can be associated with distinct pain pathways. For instance, a report comparing pain behaviours in rats with OA induced by intra-articular injection of mono-iodoacetate (MIA) *vs*. partial meniscectomy (MNX) revealed persistent, robust secondary mechanical allodynia and hyperalgesia in MIA rats, but milder and slower-onset allodynia, without hyperalgesia, in partial MNX rats (14). In addition, MIA rats had more severe weightbearing deficits throughout the 4-week study. The severity of joint damage was similar in both models, leading the authors to conclude that "the type of joint damage rather than the absolute extent is important in generating a behavioural pain response".

This hypothesis is testable by using different models that differentially display specific aspects of structural joint pathology. For example, collagenase-induced OA is associated with synovial inflammation more so than the destabilisation of the medial meniscus (DMM) model (15), and these models are associated with distinct pain behaviours: mechanical allodynia occurs in both models, but heat hypersensitivity in the hindpaw can only be detected in collagenase-induced OA (15, 16). Since the molecular and neuronal pathways involved in mediating these types of hypersensitivity are distinct, studies in models that capture different aspects of the human disease clearly offer an opportunity for comparative analysis of pain mechanisms associated with different aspects of OA. Such observations also underscore the heterogeneity of OA as a disease and indicate that a "one size fits all" approach to analgesia will not be effective.

Furthermore, an important consideration when modeling rheumatic diseases and associated pain is that these diseases are mostly chronic and progressive in nature. Hence, pain behaviours and mechanisms at play may change depending on the stage of disease. This has been demonstrated in surgical models of OA that mimic the slowly progressive nature of the disease, such as the DMM model (17). For example, we have recently shown that inhibition of nociceptors reduced mechanical pain in early, but not late stages of this model, while morphine blocked pain at all phases of the disease (18). Temporal effects have also been reported following partial medial meniscectomy, where mice develop pain hypersensitivity in two phases: an early phase, which is responsive to diclofenac and may be associated with postoperative inflammation; and a later phase 7 weeks after surgery, when overt cartilage damage is present, and the hypersensitivity is no longer responsive to diclofenac but responded to morphine (19).

Likewise, increasing efforts to unravel the contribution of different pain mechanisms in models of RA are revealing that different methods of induction result in different pain behavioural patterns (20). Importantly, temporal effects are also clearly present in these models;

studies in chronic models of inflammatory arthritis, the collagen-antibody-induced arthritis (CAIA) and the K/BxN serum transfer models, have shown that pain sensitisation can persist long after the inflammation has resolved (21, 22), reflecting the clinical experience in some RA patients where there is persistent pain in spite of adequate suppression of the inflammation (see Walsh *et al*. in this supplement).

The field of neurobiology has witnessed tremendous advances in the understanding of basic pain mechanisms. Studies using ever more advanced genetic, molecular, neurobiological, behavioural, and imaging techniques are revealing increasingly detailed pathways and mechanisms, many of which are clearly "druggable" and could potentially be modulated with targeted interventions (23). Currently, information on how these pathways and mechanisms contribute to pain in rheumatic disease is largely absent.

In conclusion, a sophisticated and disease-specific approach to animal modelling may be very informative and will likely aid in developing tools for identifying specific pathways contributing to different types of pain and sensitisation in specific diseases, and this at specific stages. For instance, findings from such models may contribute to the development of biomarkers associated with a specific stage or pain mechanism, or help identify early determinants of progression to the next stage. A clear understanding of the neuronal substrates underlying rheumatic pain using cutting edge neurobiological techniques in disease-specific models will hopefully help to usher in novel therapeutic agents targeted to specific pain mechanisms that operate at different points during disease development.

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