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Modelling pain in post-traumatic osteoarthritis of the knee

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Osteoarthritis (OA) pain represents a major unmet medical need. OA is the most common joint disorder, affecting primarily the knees, hips, hands, and spine [7]. A recent American College of Rheumatology task force concluded that pain is the most common symptom of patients with rheumatic disorders, including OA, and pain is the major reason for seeking medical care [10]. Available pharmacologic approaches include NSAIDs or analgesics, and intra-articular viscosupplementation or steroids, which can alleviate mild-to-moderate pain in OA. Treatment of severe OA pain remains inadequate and pain is a major reason for seeking surgical intervention. The number of total joint replacements in the United States keeps increasing, with a projected 600,000 hip and 1.4 million knee replacements in the year 2015 [5]. This clearly represents an enormous economic burden.

In spite of the major impact of OA pain on quality of life and health care management, OA and pain researchers alike have a limited understanding of the origins and mechanisms of pain generation in OA. “Few studies have examined pain behaviours in relevant murine OA models,” Dr. C. Knights and co-authors point out in their work in the current issue of *Pain* [6]. Their study set out to characterize a time-course of a comprehensive range of pain-dependent measures and the effect of analgesic drugs in a surgical model of OA in C57BL/6 mice, up to 12 weeks post surgery. This approach is important for several reasons, discussed herein.

For epidemiological purposes, OA is defined as radiographic OA (joint space narrowing due to cartilage loss, subchondral bone sclerosis, and osteophytes). Population studies indicate discordance between severity of radiographic changes and severity of pain [2]. This has been mostly studied for the knee. Other imaging techniques, such as magnetic resonance imaging (MRI) have related structural changes including bone marrow lesions, sub-articular bone attrition, synovitis and effusion to knee pain, and there is ample evidence that bone marrow lesions are associated with knee pain, although the mechanism is unclear (reviewed in [3]).

OA is, however, a slowly progressing pathology, and it is clear that structural joint changes precede radiographic and MRI findings, possibly by many years (during which time subjects may or may not have pain). During this time, molecular and cellular changes in joint tissues may affect the joint’s sensory innervation and thus trigger changes that may ultimately lead

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to chronic pain. It is unknown which tissues in the joint contribute to pain generation and how they interact with innervating nociceptors. OA affects all tissues in the joint, including the subchondral bone, the synovium, the fat pad, the ligaments (all of which are richly innervated), and of course the cartilage. Although articular cartilage is aneural and not likely the direct source of pain, it is a tissue made up of an exquisite network of extracellular matrix molecules that are degraded and released into the synovial cavity during the OA pathological process. We can assume that matrix fragments will interact with nociceptors in the synovium and elsewhere. In fact, episodic synovitis is a frequent feature of OA, and inflammatory mediators are part of the pathology.

When or how OA of the knee starts is unknown. We do know, however, that joint trauma is a predisposing factor. On long-term follow up, anterior cruciate ligament (ACL) injury and/or meniscal damage, which frequently occur in athletes, are associated with knee OA and pain, even in younger adults – often referred to as “young people with an old knee” [8]. The murine model used by Knights and co-workers is a model of post-traumatic OA (partial medial meniscectomy), which offers the advantage that it progresses slowly over 12 weeks post surgery, thus allowing for a careful characterization of pain behaviours over time. The new model contrasts with other rodent models that have been used to study OA pain, including the rat medial meniscal tear model and the rat monosodium-iodo-acetate (MIA) model [1]. Both are quite aggressive, which precludes studying long-term temporal changes in pain behaviours in relation to structural joint changes. In the latter model, MIA is injected intra-articularly into the rat knee, where it interferes with cell metabolism, resulting in chondrocyte cell death and eventual histological changes that resemble human OA. The MIA model is widely used by pain researchers and has offered many novel insights, but it has a major disadvantage: killing the chondrocytes effectively eliminates one of the major players in OA pathophysiology. Additionally, it can be expected that MIA, especially at high doses, may also affect other cells in the joint, including sensory neurons.

In their current work, Knights et al demonstrate that, following partial medial meniscectomy, female C57BL/6 mice develop pain hypersensitivity in two phases: an early phase, 1–2 weeks after surgery, which is responsive to diclofenac, and appears to be associated with postoperative inflammation. A later phase occurs approximately 7 weeks after surgery, when overt cartilage damage is present. The hypersensitivity in this later phase, including vocalization in response to knee pressure, was no longer responsive to diclofenac, but responded to morphine. Pain levels during the later phase fluctuated and could be unmasked by the endogenous opioid receptor antagonist, naloxone, indicating that reduced pain was due to endogenous opioids. A limitation of the study is that histological assessment of OA pathology was restricted to cartilage degeneration. Nevertheless, studies like these pave the way for assessment of detailed correlations between pain-dependent measures and histopathological changes in all joint tissues, including the subchondral bone and the synovium. In addition, the slow progression of this model, as in another murine model of post-traumatic OA, the destabilization of the medial meniscus [4,9], allows for assessing temporal changes in joint innervation and dissecting molecular pathways of pain generation. Availability of genetically modified mice should enable the identification of key mediators of pain generation in post-traumatic OA.

While chronic pain associated with OA is the result of a complex interaction between local events in the joint, peripheral and central sensitisation, the brain, psychological and social factors, and comorbidities, appropriate animal models such as these will help us understand early events in the damaged joint, and the interactions between joint tissues and the nervous system. Studies in these models should provide novel insights into pain development in association with structural changes in post-traumatic OA, and offer opportunities for early intervention.

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