Cell-cell interactions in joint pain: rheumatoid arthritis and osteoarthritis

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Abstract
Rheumatoid and osteoarthritis are chronic conditions generating joint pain for which better management is required. We argue that a better understanding of the cell-to-cell interactions occurring within the joint will enhance mechanistic understanding of joint pain and could lead to new therapeutic avenues being explored.

Text
This Pain Pictured article describes the cell-cell interactions involved in the pathology and pain of rheumatoid arthritis (RA) and osteoarthritis (OA), conditions in which improved pain management is considered key by patients and drives clinical decision making [23,25]. According to the Global Burden of Disease Study 2017, RA had a global prevalence of ~20 million individuals and knee and hip OA ~300 million, both conditions being more common in females than males with prevalence increasing with age, peaking at 60-64 years of age [38,39]. Although both RA and OA cause joint pain with overlap of cellular and inflammatory mediators, there are also key differences in pathology and presentation. For example, RA is an autoimmune disease typically first affecting small joints (i.e. finger/toe joints) but can progress to larger joints, such as the knee, whereas OA pathogenesis involves biomechanical and inflammatory processes affecting multiple joint structures that ultimately lead to structural deterioration with the knee being most commonly afflicted.

Although joint pain is more diffuse than cutaneous pain, most joint structures, including bone, synovium, ligaments, tendon synovial sheaths, infrapatellar fat pad, and menisci are innervated; notably, healthy adult articular cartilage is aneural. Approximately 80% of joint innervating fibers are unmyelinated (a combination of afferent and sympathetic fibers), the remaining 20% being predominantly myelinated Aδ-fibers [24,29]. The majority of afferent fibers are nociceptors, a large population being “silent” nociceptors that only become active following sensitization [41].

Joint pathology in RA is characterized by synovial inflammation, cartilage degradation, bone erosion and bone marrow lesions. Synovioctyes proliferate, developing a proinflammatory and catabolic phenotype, whilst numerous immune cells (macrophages, T cells, B cells, plasma cells, mast cells, dendritic cells and neutrophils) infiltrate the synovium and synovial fluid (SF) where they produce proinflammatory mediators, catabolic factors, and chemoattractants that recruit additional immune cells [10,19]. The combined infiltration of T cells, B cells and plasma cells that drive autoimmunity and local autoantibody production is a feature unique to RA when compared to OA. In the OA joint, changes include: alternations in chondrocyte phenotype, density and activity – cartilage erosion is followed by chondrocyte hypertrophy and generation of matrix degradation products alongside proinflammatory mediator secretion; infiltration of mast cells, macrophages and CD4+ lymphocytes; synoviocytes proliferate (albeit to a lesser extent than in RA) and release proinflammatory mediators; and changes in subchondral bone turnover due to increased osteoblast and osteoclast activity result in a combination of sclerotic bone, osteophyte formation and subchondral bone marrow lesions with altered vascular and neuronal innervation [5,25,35,46].

Cell-cell interactions occur in RA and OA primarily via release of soluble mediators, the power of which is demonstrated by acellularized human OA-SF sensitizing mouse knee-innervating sensory neurons, thus highlighting the importance of soluble mediators driving cell-cell interactions and pain in arthritis [11]. With regard to the specific mediators that drive pain in arthritic joints, there is some overlap between those involved in RA and OA, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin production and provide relief from pain and inflammation in both conditions. It should be noted however that pain can occur even when inflammation is medically controlled [4]. In both RA and OA, factors that are locally produced in joints that could potentially act via nociceptor

expressed receptors include tumor necrosis factor α (TNFα) [26], interleukin 1β (IL-1β) [31], IL-6 [16], and IL-17 [15]. While, targeting TNFα, IL-1β, and IL-6 is efficacious in treating RA, this has not yet been replicated for OA, even though all are implicated in OA pathogenesis. In contrast, nerve growth factor (NGF), which causes hyperalgesia [30], is reportedly elevated in RA and OA SF, and clinical trials highlight anti-NGF antibodies as a promising therapeutic for treating OA pain [7,42], but have yet to be investigated in RA focused clinical trials.

Specifically in OA, toll-like receptor 2 (TLR2), which is activated by a 32-amino-acid aggrecan fragment found in OA-SF, has been highlighted as a potential analgesic target [20,33]. In addition, nociceptors that express voltage-gated sodium channel 1.8 ($Na_V1.8$) and innervate osteochondral channels have been demonstrated to play a key role in pre-clinical OA models [46], which makes this nociceptor subset a promising therapeutic target considering that nociceptors innervating osteochondral channels are associated with OA pain in humans [5].

Multiple studies indicate that SF pH is decreased in RA, more so than in OA [14,18,21,22], and accordingly, ion channels activated by extracellular protons, such as acid-sensing ion channel 3 (ASIC3) [27,43] and transient receptor potential vanilloid 1 (TRPV1) [9], are linked to mechanical hypersensitivity in experimental arthritis models. It is however unclear if protons for one specific cell type are responsible for these effects. Additionally, lipid mediators linked to RA and OA joint inflammation, such as lysophosphatidylcholine ,can directly activate ASIC3 [32]. Lastly, in RA, autoantibodies directly stimulate nociceptors by forming immune complexes with cartilage proteins like collagen type II and then activating neuronally expressed Fcγ receptor I [8,36]; autoantibodies can also stimulate other cells to produce pain mediators like CXCL1/2 [45].

In addition to peripheral mechanisms, there are also central changes in RA and OA pain processing [17,28] and there is substantial debate in the field as to which is clinically more important, but therapeutic targeting of peripheral events is likely to be simpler and associated with fewer side effects. With regard to central pain processing, in preclinical RA models, expression of TLR4 by spinal microglia and its endogenous ligands, such as HMGB1, has been directly linked to pain-like behavior in a sex and cell specific manner [1,2]. Moreover, TLR4 expressed by local joint immune cells contributes to joint HMGB1-mediated hypersensitivity in males to a larger extent than in females, while TLR4 on nociceptors participates in HMGB1-mediated joint pain in both sexes [37]. Similarly, in preclinical OA models, increased spinal microglia proliferation and activation correlates with pain [40,44]. However, neuroimmune interactions are not restricted to the proximal and distal nerve endings of primary afferent neurons, a key role for macrophage infiltration into the dorsal root ganglia also being illustrated in both OA and RA pain [6,34].

In summary, RA and OA pain involve a multitude of cell-cell interactions and a plethora of proinflammatory mediators, both peripheral and central mechanisms being involved. Increasing mechanistic understanding of the cell-cell interactions occurring and the mediators involved will hopefully lead to identification of new therapeutic strategies, including the potential use of gene therapy to modulate knee-innervating sensory neurons [12].

Conflicts of interest
The authors have no conflicts of interest to declare.

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