



Commentary

Do synovial fibroblast subsets shape pain and vice versa?

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Single cell analysis is one of the most impactful techniques developed in recent years. It has opened up the possibility of distinguishing previously undiscovered functional and, in particular, pathologically important subpopulations of cell types in various tissues and diseases. Especially in very heterogeneous tissues such as joint synovial tissue, where immune cells and stromal cells are highly interconnected, single-cell RNA sequencing (scRNA-seq) has provided important new insights into physiological and pathological cellular processes. Several publications have described different subpopulations of synovial fibroblasts and have revealed functional differences not only between fibroblasts found in the lining and sublining layers of the synovium, but also between different sublining synovial fibroblast populations. Some of these sublining synovial fibroblasts have been described as particularly increased in rheumatoid arthritis (RA) [1].

In a recent study published in *EBioMedicine*, Nanus et al. used bulk transcriptome analysis and scRNA-seq to analyse differences between synovial tissues isolated from painful and non-painful areas in joints from people with osteoarthritis (OA) [2]. OA is one of the most common rheumatic and musculoskeletal diseases worldwide and represents an immense economic burden. Nowadays, it is widely acknowledged that OA is not just a passive degeneration of the cartilage, but that apart from the cartilage other joint tissues such as the synovium, ligaments, joint capsule and subchondral bone are actively involved [3]. Pain is the main symptom of OA, leading to disability and high personal burden. An effective and safe strategy for pain management in OA is still lacking, and patients often develop a chronic pain condition. Better knowledge on local pain mechanisms and molecular pathways is an important step towards developing targeted medication for OA pain.

Interestingly, in their analysis Nanus and colleagues found specific fibroblast subpopulations that mainly appeared in the synovium from painful sites of the joints. Furthermore, they also found substantial differences in the fibroblast subpopulations derived from painful synovium

in early versus late-stage OA. These findings suggest that specific fibroblast phenotypes are strongly associated with pain and that these 'pain fibroblast' phenotypes are modulated during the course of the disease. Now, do these fibroblasts modulate OA pain, does pain modulate fibroblast phenotypes, and what role do other cells play?

To address the question of whether synovial fibroblasts influence the development of OA pain, the authors showed that supernatants from fibroblasts isolated from painful areas of the joint synovium had a positive effect on survival of dorsal root ganglion neurons and promoted neurite outgrowth. However, from the various neurotrophic factors that were measured in the supernatants of fibroblasts of painful versus non-painful areas, none stood out to be significantly more produced, even though slightly elevated levels were found in almost all of them. Unfortunately, nerve growth factor, which has been recognized as a key driver of pain in OA [4] and is strongly produced by synovial fibroblasts [5], was not measured.

In this and previous studies, a positive correlation between synovitis and pain in OA was found, whereas correlations of pain with structural damage are weak [3]. Thus, it is feasible to assume that in addition to mechanical factors, pro-inflammatory cytokines produced by cells in the inflamed synovium activate nociceptors in the affected joints. Cytokines such as TNF, IL-1, IL-6, and IL-17A were suggested to be able to indirectly activate nociceptors, whereas eicosanoids can directly stimulate neurons [6]. Interestingly, in early OA inflammatory pathways and regulators were more prominent than in late-stage OA, while eicosanoid pathways were active in fibroblast populations in both early and late OA pain. This could mean that in early stages of OA indirect activation of nociception via inflammatory cytokines produced by the activated synovium plays a bigger role than in late-stage OA. Accordingly, only one 'pain fibroblast' subpopulation was identified in late-stage OA, compared to four different 'pain fibroblast' subpopulations in early OA. Since synovial fibroblasts are not the main producers of the above-mentioned pain-associated cytokines in the synovium, but are tightly interconnected with immune cells, in particular macrophages within the synovium, it might be that co-activation of fibroblasts and other synovial cells promotes pain in the early phases of OA. Accordingly, increased levels of TNF and IL-1 were found in early OA synovium compared to late OA [7]. In the current study, only synovial fibroblasts were analysed in the scRNA-seq approach, so that differences in immune cell activation between early and late-stage OA and between painful and non-painful synovium still has to be elucidated.

In the context of chronic pain diseases, such as OA, it is important to understand that the perception of pain is not limited to the

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transmission of the signal by nociceptive neurons to the central nervous system. Acute pain events trigger various local and central feedback mechanisms that influence the perception of pain [4]. Locally, stromal and immune cells can secrete neuromodulatory factors and nociceptors can increase their production of neuropeptides to adapt pain thresholds. In the course of pain modulation, distal nerve endings secrete neuropeptides such as substance P and calcitonin gene-related peptide. In some OA patients, central sensitization of pain with increase excitability of neurons in the dorsal root ganglion was described [8]. This points to alterations in nociception and disturbances in the pain regulatory mechanism in OA patients. Indeed, alterations in the structure of brain areas that belong to the descending pain modulatory system were found in patients with OA [9]. Thus, it can be speculated that the differences in "pain fibroblasts" between early- and late-stage OA patients may be related to the effects of chronic pain-modulating mechanisms on local synovial cells. Up to now, little is known about whether and how chronic pain affects local stromal and immune cells. Future studies using advanced -omics technologies to analyse the crosstalk between stromal, immune, and neuronal cells could provide novel therapeutic targets and interesting insights into the mechanisms involved in chronic pain disorders like OA.

Contributors

CO conceived and wrote this invited Commentary.

Declaration of Competing Interest

The author has no conflicts of interest to disclose.

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