RHEUMATOID ARTHRITIS

Functionally distinct fibroblast subsets in RA

> patients with RA had an expanded population of synovial FAPα⁺THY1⁺ fibroblasts

Fibroblasts are important in the pathogenesis of immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA). In a new study published in *Nature*, researchers have for the first time described two functionally and anatomically distinct populations of fibroblasts that affect different aspects of arthritis, namely inflammation and damage.

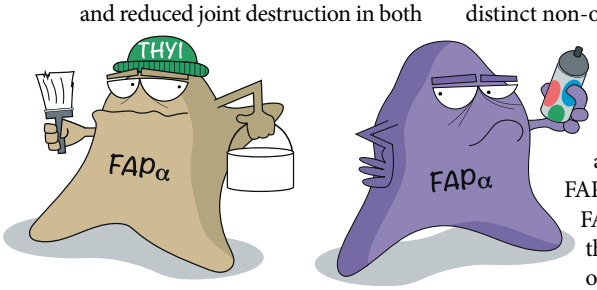
"Fibroblast subsets have been proposed for some time on the basis of site and disease-specific differences in surface markers as well as epigenetic differences in fibroblasts taken from different anatomical sites," explains corresponding author Christopher Buckley. "However, it was unknown whether the processes of inflammation and tissue damage, mediated by fibroblasts, are always coupled (reflecting cellular plasticity residing within a single fibroblast population) or instead are uncoupled and mediated by different subsets of fibroblasts."

On the basis of preliminary findings, the researchers began by characterizing the expression of fibroblast activation protein-α (FAPα) during K/BxN serum transfer-induced arthritis (STIA) in mice. FAPα was expressed in fibroblasts in both the synovial lining and sub-lining layers and its expression increased during the course of arthritis, correlating with the severity of ankle joint swelling. Selective depletion of FAPα-expressing cells attenuated synovial inflammation and reduced joint destruction in both a resolving and a persistent model of STIA.

Buckley and colleagues found that thymus cell antigen 1 (THY1) expression could distinguish between FAPα-expressing fibroblasts in the synovial sub-lining (FAPα⁺THY1⁺ cells) and lining layers (FAPα⁺THY1⁻cells). Interestingly, the number of FAPα⁺THY1⁺ cells in the synovium correlated with the severity of joint inflammation, whereas the number of FAPα⁺THY1⁻ cells correlated with cartilage damage.

To investigate functional differences between these two anatomically distinct subsets, the researchers performed single-cell sequencing on non-immune synovial cells isolated from the inflamed joints of these mice. They identified five distinct subgroups of fibroblasts: four in the sub-lining and one in the lining layer. Similar analysis of synovial fibroblasts from patients with RA also revealed five subgroups, three of which were homologous with the mouse subgroups.

As before, THY1 expression could discriminate between the mouse subsets by anatomical location. The FAPα⁺THY1⁺ subsets had an immune effector phenotype, expressing genes encoding cytokines and chemokines, whereas the FAPα⁺THY1⁻subsets had a bone effector phenotype, expressing genes associated with cartilage and bone degradation, supporting the idea of distinct non-overlapping functions.



Credit: S. Harris/ Springer Nature Limited

To ascertain the in vivo contribution of these subsets, the researchers adoptively transferred FAPα⁺THY1⁺ cells or FAPα⁺THY1⁻cells into the inflamed joints of mice during STIA. Injection of FAPα⁺THY1⁺ cells exacerbated joint swelling and increased synovial infiltration, but had little effect on destruction of bone or cartilage. By contrast, injection of FAPα⁺THY1⁻cells increased osteoclast activity and structural joint damage, but had no effect on joint inflammation.

Hence, the findings indicate that FAPα⁺THY1⁺ cells, residing in the sub-lining layer, promote inflammation, whereas FAPα⁺THY1⁻cells, residing in the lining layer, promote bone and cartilage damage in arthritis. Buckley proposes that these different subsets could be responsible for different forms of arthritis. Interestingly, the investigators found that patients with RA had an expanded population of synovial FAPα⁺THY1⁺ fibroblasts compared with patients with osteoarthritis (OA), which correlated with markers of inflammation.

"The importance of this work cannot be overstated," explains Peter Paul Tak, an expert in the pathogenesis and development of new therapeutics for IMIDs who was not involved in this study. "It opens up a new field of research on the role of these distinct fibroblast subsets during different stages of chronic inflammatory diseases, including IMIDs other than RA, and research on the effects of therapeutic targeting of distinct fibroblast subsets in relationship to stage of the disease."

"Current treatments for RA and other IMIDs target immune cells either directly or by trying to disrupt the signals that attract the cells to the joint. No treatments directly target fibroblasts," explains Adam Croft, first author of the study. "These findings mean that we now have a clear rationale for developing drugs that can target joint fibroblasts directly and provide more effective treatment for persistent disease."

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