Two types of fibroblast drive arthritis

Fibroblasts are a type of cell found in all tissues of the body. They help to maintain the structural integrity of connective tissues by secreting the protein collagen and other components of the material that comprises the extracellular matrix, which provides support for neighbouring cells. Despite their crucial role in maintaining a healthy tissue architecture, it is becoming increasingly clear that fibroblasts can also contribute to inflammation and tissue injury in a variety of autoimmune diseases, including rheumatoid arthritis—a condition characterized by persistent inflammation, bone erosion and the destruction of cartilage in the joints. On page 246, Croft et al. report evidence indicating that the progression of rheumatoid arthritis is driven by two populations of fibroblast that have distinct gene-expression profiles, located in different regions of the joint and contributing to different aspects of the disease.

It was previously unclear whether a single population of fibroblasts contributes to the destruction of joints that is observed in rheumatoid arthritis, or whether different fibroblast types with distinct functional activities are involved, as seems to be the case in other diseases in which fibroblasts have key roles. To study this, Croft and colleagues examined samples of the synovial membrane (layers of cells that surround a joint) from people with rheumatoid arthritis. They found that high expression of the protein FAPα in these tissues was strongly linked with the structural integrity of connective tissues of the body. They help to maintain a healthy tissue architecture, it is becoming increasingly clear that fibroblasts can also contribute to inflammation and tissue injury in a variety of autoimmune diseases, including rheumatoid arthritis—a condition characterized by persistent inflammation, bone erosion and the destruction of cartilage in the joints. On page 246, Croft et al. report evidence indicating that the progression of rheumatoid arthritis is driven by two populations of fibroblast that have distinct gene-expression profiles, located in different regions of the joint and contributing to different aspects of the disease.

The authors investigated whether there were any other indications that these two cell populations represented unique subsets that have distinct functional roles. Using their mouse model and performing single-cell RNA sequencing of cells isolated from the synovial membrane at the peak of inflammation (which were isolated in a way that excluded immune cells), the authors identified five cellular groupings that had distinct gene-expression profiles. One group corresponded to the FAPα-expressing, Thy-1-lacking cells in the LL and the other four were distinct subpopulations of the FAPα- and Thy-1-expressing cells in the SL. These SL cells expressed many genes that encode signalling molecules called cytokines, which are associated with immune-system function and inflammation. By contrast, the cells in the LL expressed genes associated with cartilage and bone erosion. These distinctive patterns of gene expression suggested that the two cell populations might perform non-overlapping functions in vivo.

To assess the functional role of the fibroblasts, the authors used their mouse model of arthritis to deplete fibroblasts during the initiation and maintenance phases of the disease. The depletion of all FAPα-expressing fibroblasts led to a substantial reduction in the number of cells in the synovial membrane, suggesting a general reduction in inflammation. The loss of FAPα-expressing cells also correlated with a reduction in the thickness of the ankle joint compared with that in animals in which fibroblasts had not been depleted. Strikingly, the reduction in synovial inflammation and joint destruction, which was quantified by assessing the degree of loss of cartilage and bone, was observed whether the fibroblasts were depleted early or late in the course of the disease. This protection from disease progression correlated with a loss of both fibroblast populations, but with a loss of pericytes, a type of fibroblast found associated with blood vessels. The reduced inflammation was accompanied by a decrease in immune cells such as neutrophils, monocytes...
and macrophages, which are major drivers of inflammation. Interestingly, macrophages in the synovial membrane of FAPα-depleted mice had a pattern of gene expression that is characteristic of an anti-inflammatory state. This raises the question of whether disease-associated macrophages are a source of pro-inflammatory cytokines, and also whether these cells acquire an anti-inflammatory profile when numbers of FAPα-expressing cells are reduced. However, this was not specifically confirmed by the authors.

To test the individual contributions of the two fibroblast populations directly, the authors isolated cells that either expressed or lacked Thy-1, and injected them into the inflamed joints of arthritic mice. Mice that received Thy-1-expressing fibroblasts developed more-severe inflammatory arthritis, but not greater bone or cartilage destruction than was the case for animals that did not receive a cellular transplant. By contrast, injection of fibroblasts lacking Thy-1 did not affect the level of inflammation, but bone erosion was greater than it was in animals that had not received a transplant. The authors concluded that the subset of Thy-1-expressing fibroblasts drove inflammation by producing cytokines, whereas the fibroblast subset lacking Thy-1 contributed to bone and cartilage destruction.

To investigate whether their findings might have relevance for human disease, the authors examined samples of cells from the synovial membrane of people with either rheumatoid arthritis or osteoarthritis — a form of arthritis characterized by joint damage but little or no inflammation. They found that people with rheumatoid arthritis had a larger population of fibroblasts that express FAPα and Thy-1 than did people with osteoarthritis. Future studies should determine whether fibroblasts that express FAPα but lack Thy-1 are present in greater numbers in the synovial LL of people with rheumatoid arthritis or osteoarthritis than in the LL of healthy people, because this was not specifically examined by the authors, but is predicted by their model.

These exciting findings raise the possibility that clinical strategies might be developed for the selective depletion, targeted replacement or functional conversion of fibroblast subpopulations. Such approaches might one day provide treatment options not just for rheumatoid arthritis, but for a wide range of chronic inflammatory diseases.

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