

## Why should Rheumatologists care about fibroblasts?

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Have you ever wondered why some inflammatory diseases resolve while others persist? For example acute gout is a self-limiting disease whereas rheumatoid arthritis persists. A frozen shoulder (adhesive capsulitis) nearly always “gets better” while osteoarthritis does not. Furthermore a common feature of many rheumatic diseases, and one that clinical rheumatologists rely on to help them make a diagnosis, is that most forms of arthritis have a predilection for particular joints, and even tendons rather than the joint itself. For example osteoarthritis and psoriatic arthritis often involve the distal interphalangeal joints, whereas rheumatoid arthritis is more often symmetrical and more commonly affects the MCP joints. In contrast ankylosing spondylitis mainly targets spinal ligaments and enthesial tissue. The cellular and molecular basis for disease persistence and tissue tropism has until now remained enigmatic but recent findings suggest that tissue resident stromal cells such as fibroblasts provide an unexpected answer to these questions.

(1)

Fibroblasts are mesenchymal cells that provide the cellular infrastructure for organs, as well as lining mesodermal membranes such as the synovial membrane. They are mostly involved in the deposition and resorption of the extracellular matrix (ECM) and help maintain tissue homeostasis. Fibrotic diseases such as systemic [sclerosis](#) have typically been thought to be driven by pathogenic fibroblasts. However, fibroblasts are far more than just structural cells involved in pathology (2). They are sensitive to environmental changes and both produce and respond to a range of cytokines and chemokines. They respond in a very specific manner to different stimuli and actively influence not only the composition of the ECM but also the degree of inflammation within and destruction of barrier membranes such as the synovium (2)

Under inflammatory conditions, fibroblasts act as organ-specific, innate immune system sentinel cells where they are involved in the switch from acute resolving to chronic persisting inflammation (3). For example, fibroblast-like synoviocytes (FLS) play a critical role in the pathogenesis of RA and possess a characteristic, invasive, and activated phenotype

(4). In addition to contributing to the recruitment and emigration of inflammatory cells to and out of the joint, they modulate the survival and behaviour of infiltrating leucocytes. It is now clear that fibroblasts can exist in discrete subsets, some of which are pro-inflammatory while others, more functionally similar to mesenchymal stromal cells (MSC), are anti-inflammatory and regulate tissue homeostasis and organ repair (5). More importantly, FLS are crucial components in the hyperplastic lining layer and in cartilage destruction. New data raise the possibility of epigenetically programmed aggressive cells “spreading” arthritis from inflamed to uninfamed joints in the early stages of arthritis, but at the same time offering the possibility of specifically targeting stromal subpopulations of choice. (6).

Work over the last decade has demonstrated that fibroblasts modify the quality, quantity and duration of leucocyte accumulation within tissues. They also contribute to the resolution of inflammation by normalizing chemokine gradients, thereby allowing infiltrating leukocytes to leave the tissue through the draining lymphatics. We have proposed that inflammation is contextual and since fibroblasts help define tissue topography we have suggested that fibroblasts represent an attractive, site specific, therapeutic target (7).

The introduction of biologic treatments that deplete leucocytes and their secreted products has led to a step-change in the management of IMIDs. However these therapies do not reverse tissue damage and do not result in a cure. A significant proportion of patients continue to have stubbornly resistant disease. Moreover many patients, in whom clinical remission has been achieved, subsequently relapse once treatment is withdrawn, suggesting that additional therapeutic targets, such as fibroblasts that are responsible for complete resolution of inflammation, remain to be discovered.

Inflammation results from the complex interaction between haematopoietic and stromal cells. Yet almost all current therapies target haematopoietic cells and ignore stromal cells, such as fibroblasts. Therefore an understanding of the origins and functional consequences of “pathogenic fibroblasts” as opposed to their physiological counterparts provides the scientific basis for new therapies based on reversing the persistence of disease. For example fibroblasts express Toll-like Receptors and other pattern recognition receptors. In RA they express a specific pattern of coding and non-coding (small and long) RNA that distinguishes them from non-RA synovial fibroblasts and are endogenously activated due to epigenetic imprinting for tissue destructive pathways (8). Like an anti-cancer tissue response, it is tempting to propose that inflammation creates an anti-tissue response that spreads from the original site to distant predisposed sites where they are particularly susceptible to immune attack. Strikingly, fibroblasts maintain their diversity, topographic

differentiation and positional memory in culture. Emerging data have shown site, stage and disease specific differences in the coding and noncoding fibroblast transcriptome. (9).

Despite their biological importance, remarkably little is known about how fibroblast numbers and subsets change during inflammation. Difficulties in accessing patients with very early disease, sampling the tissue involved and the lack of good fibroblast markers have all proved obstacles to such work (1). However, stromal cells such as fibroblasts are a functionally heterogeneous group of cells with some displaying pro-inflammatory and destructive properties, whereas others are immune-regulatory and help facilitate tissue repair. This has led to a therapeutic dilemma. Which cells should be targeted or replaced and which should be retained? A clear understanding of the biology and significance of fibroblast heterogeneity is therefore essential to provide a coherent rationale for their use in the future treatment of IMIDs. In the meantime fibroblasts ~~s biology~~ rather like Cinderella haves joined leucocytes and their cell products at the “Rheumatology ball”.

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