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The fibroblast as a therapeutic target in rheumatoid arthritis

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Significant advances have been made in the last 5 years that have finally allowed investigators to start targeting stromal cells such as fibroblasts in inflammatory disease.
Rheumatoid arthritis is a prototype inflammatory disease, in which fibroblasts maintain the persistence of inflammation in the joint underpinned by a unique pathological phenotype driven by multiple epigenetic modifications.The step changes that are enabling the development of such therapies are an improved understanding of the mechanisms by which fibroblasts mediate persistence and the discovery of new markers that identify discrete functional subsets of fibroblast cells that have potential as disease-specific therapeutic targets.

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Introduction

Writing this review 10 years ago would have been highly speculative. Such an undertaking is now however timely, as a result of important advances in our understanding of stromal cell biology. Fibroblasts are the largest constituent group of stromal cells, a classifier that also encompasses vascular and lymphatic endothelial cells, pericytes and arguably tissue resident leukocytes such as macrophages and dendritic cells.

The first major advance is the understanding that fibroblasts retain fundamental signatures that govern their behaviour. The most important of these governs spatial identity [1], however fibroblasts also develop persistent, disease-specific phenotypes that drive the expression of organ specific disease. Fibroblasts therefore represent potentially specific targets lacking the familiar adverse effects of immunosuppression observed with treatments based upon classical innate and adaptive immune systems.

Developments in rheumatology are rapidly following established work in cancer medicine directed at 'cancer associated fibroblasts' within the tumour stroma, that are known to play vital gatekeeping roles in tumour growth and metastasis [2]. Historically, the targeting of immune system cells has been greatly facilitated by cell and lineage specific markers such as the cluster differentiation (CD) marker system, while markers for specific subpopulations of fibroblasts have eluded investigators. The final piece of the jigsaw allowing us to modulate fibroblast-directed pathology is only now coming into place, as new markers that subdivide stromal cells based on both anatomy and function are being recognised and developed.

This review will describe strategies for targeting fibroblasts that are in use or shortly expected to come into use, paying particular attention to recent developments.

Why target fibroblasts?

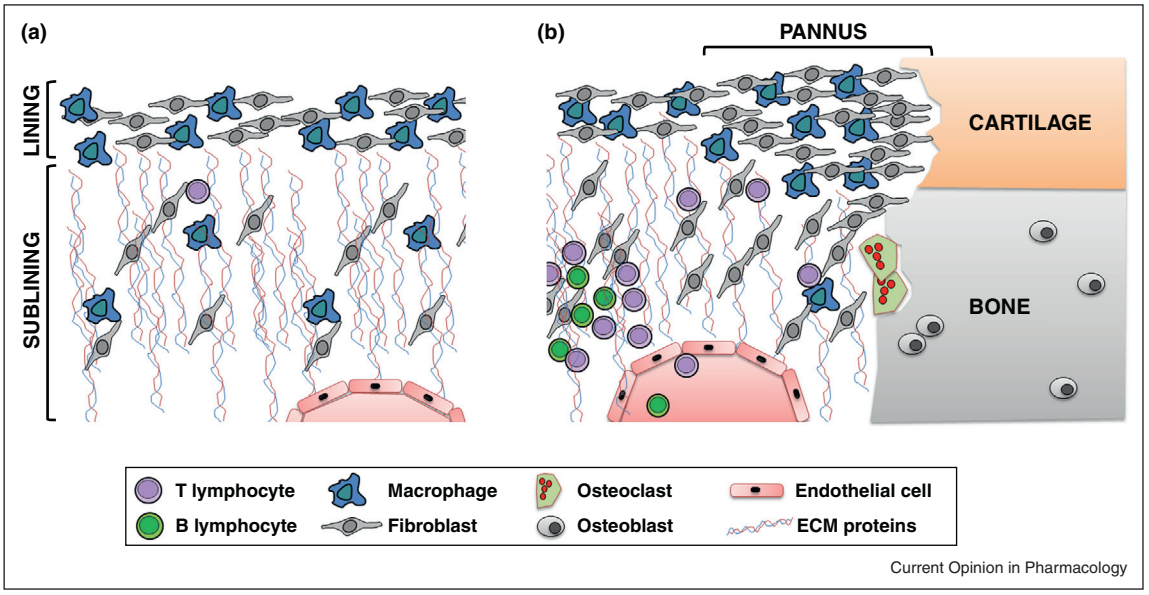
Inflammation in RA

Encompassing the entirety of RA pathogenesis is beyond the scope of this review (see [3]). Within the inflamed synovium, multiple leukocyte subpopulations have been implicated in the generation of networks of inflammatory cytokines and chemokines that lead either directly or indirectly to swelling, pain, loss of function and ultimately joint damage and deformity. These subpopulations include activated T cells, B cells, plasma cells, NK cells macrophages and dendritic cells [3]. Cell types including B cells have been targeted with biological therapies, while T cell costimulation has been blocked using CTLA4 constructs [4]. Nodal cytokines such as TNFα and IL-6 have also been targeted by biological therapies. However, even the most efficacious of current therapies are unable to cure disease, and share a remarkably similar therapeutic ceiling of response at around 70%. This suggests that other mechanisms underlying the persistence of inflammation in RA have yet to be targeted.

Synovial fibroblasts

In health the synovium of the joint is a delicate, thin structure attaching the bone and joint capsule. The 2–3 cell thick lining layer which is formed in roughly equal proportions of specialised fibroblasts and macrophages. This layer subserves a barrier function and secretes hyaluronic acid and lubricin. The sublining layer is composed of less densely packed fibroblasts and macrophages in a loose tissue matrix along with blood vessel networks (Figure 1a).

Figure 1



Pathological changes in the rheumatoid synovium. The fibroblast rich synovial lining layer undergoes dramatic hyperplasia, from only 1 or 2 cells in depth **(a)** to as many as 10–15 cells in depth **(b)**. At the articular borders the thickened synovial lining layer may become a mass of 'pannus' tissue that invades the adjacent articular cartilage and subchondral bone. The sublining layer also undergoes expansion, with infiltrates of inflammatory cells including macrophages, mast cells, T cells, B cells, plasma and dendritic cells.

The expanded fibroblast population in RA

In RA the synovial lining layer undergoes dramatic hyperplasia, sometimes reaching 10–15 cells in depth. At the articular borders the lining layer may become a mass of 'pannus' tissue (rich in fibroblasts and osteoclasts) that invades the adjacent articular cartilage and subchondral bone. The sublining layer also undergoes expansion, with infiltrates of inflammatory cells including macrophages, T cells, B cells and plasma cells (Figure 1b, Figure 3a). T and B lineage cells may remain in diffuse infiltrates, or may coalesce into more complex aggregates [5].

Evidence suggests that the expansion of fibroblast populations in the joint results primarily from inhibition of pro-apoptotic pathways, rather than large scale proliferation. This results on the one hand from decreased expression of pro-apoptotic factors such as PTEN, SEN-P1 and micro-RNA-34A, and on the other hand from increased expression of pro-survival factors including FLIP, SUMO-1 and over-activity of Ras, Myc and NF-κB pathways (reviewed in [6]).

Fibroblasts as mediators of damage and persistence in RA

Not only does the synovial fibroblast population in RA increase in size, but the behaviour of the cells becomes permanently changed, damaging the joint through enhanced secretion of matrix metalloproteinases and cathepsins that degrade cartilage and bone tissues. The persistent phenotype of these cells is evidenced by the autonomous invasion of human cartilage by RA fibroblasts in the SCID mouse model of arthritis [7]. Not only does this behaviour persist after multiple *in vitro* passages, but recent findings suggest that fibroblasts migrate to a contralateral cell-free cartilage implant, suggesting a tropism to damaged cartilage tissue [8•]. In addition, fibroblasts secrete both RANKLigand, that promotes osteoclast differentiation and activation leading to bone erosion [9], and DKK-1 that inhibits anabolic osteoblast function, preventing repair of bone erosions [10].

RA fibroblasts drive the persistence of inflammation by the coordinated expression of factors that maintain the recruitment, survival and retention of leukocyte subpopulations in the inflamed joint [11]. Cellular recruitment is mediated by enhanced expression of a broad range of inflammatory chemokines including CXCL8, CCL2, CCL5 and CXCL10, CXCL5 and CXCL1 [12–15] (Figure 2). These findings are reinforced by co-culture based flow models, in which RA fibroblasts selectively modulate endothelial cell behaviour in order to recruit specific leukocyte subpopulations [16,17].

Successful resolution of inflammatory responses requires the coordinated apoptosis of recruited immune cells. In RA apoptosis is inappropriately blocked by fibroblast derived factors: T cell survival is mediated by type I interferons [18], while neutrophils are dependent on GM-CSF production [19]. B cell survival depends upon