

Review

Fibroblast biology

Synovial fibroblasts in rheumatoid arthritis: leading role or chorus line?

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The continuing saga of the aetiology and pathogenesis of joint destruction in rheumatoid arthritis (RA) has often led to reassessment of the working hypotheses created to explain the phenomenon. Initial and current models set a protagonistic role for inflammatory and autoimmune cellular mediators in RA, and this notion has been well supported by a plethora of experimental data. However, it may have been biased by the relatively more easy access to experimental and clinical data regarding immune cell function and also, perhaps, by the overenthusiasm with which it was felt cellular immunology could explain chronic immunopathologies. Even from early investigations, however, it has been clear that for arthritis development, inflammatory and autoimmune processes actively interacted with a network of non-immune cell types, and that it was the effector activities of these cell types that resulted in cartilage and bone attack. Although, until recently, the non-immune constituents of the synovial lining were regarded as mere targets of the inflammatory milieu and as secondary players in the development of disease, more recent data provide serious grounds for considering these cells as dominant players in the aetiopathogenesis of RA. The series of reviews on synovial fibroblasts (SFs) presented in this issue of *Arthritis Research* aims to refocus attention on our current knowledge of the biology of SFs and their possible involvement in the development of RA.

One major drawback in our understanding of the role of synovial lining cells, and particularly of SFs in RA, has been the lack of information regarding the origins and functions of this cell type. Despite years of intensive RA research, it is still unclear which cell type is defined by the term 'synovial fibroblast'. In the first review article [1],

some of the characteristics of this mysterious cell type in terms of development and differentiation are discussed. Although difficult to document in culture, it seems that, physiologically, SFs comprise mesenchyme-derived populations that display heterogeneous tissue localization (intimal and subintimal), reflecting differential activation and differentiation states. An intriguing functional property of SFs may stem from their resemblance to bone marrow stromal cells: both cell types share common progenitors and display similar gene expression signatures. It is therefore likely that, similar to the bone marrow stromal cells, SFs may support or modulate the effector character of resident or blood-derived cells in the arthritic joint. This is further supported by the fact that intimal SFs are normally in minimal contact with immune cells, including macrophages and lymphocytes. Topographical separation may therefore provide a first degree of protection against deleterious SF-immune cell interactions. In a RA joint, both the localization and the interactions of SFs with leukocytes are altered, allowing for the development of effector functions and of pathogenic inflammation.

The complexity of the responses of normal, activated or RA SFs is governed by the differential signals emanating from the extracellular milieu. This complexity in responses is reflected in the differential expression profiles of adhesion molecules, cytokines and chemokines, extracellular matrix degrading enzymes and angiogenic factors that result in the response to haemopoietic and stromal cell derived factors. In the second review [2], a number of such factors known to interact with SFs either *in vivo* or following stimulation *in vitro*, which also modulate their phenotype and function, are discussed.

In response to extracellular factors, SFs themselves release a plethora of effector molecules interacting with a variety of cells and promoting matrix degradation. Several important scenarios are described in the third review [3]. First, SFs instigate leukocyte attraction and homing through the expression of chemokines like MIP-1, RANTES, interleukin-8 and interleukin-16. SFs can also support myeloid and lymphoid cell growth via the secretion of various colony stimulating factors, as well as their own growth via the production of platelet derived growth factor. However, the most classical effector function of RA SFs is their capacity to interact with the extracellular matrix and cause its degradation via the production of matrix metalloproteinases and cathepsins. This process seems to be autonomously regulated since it is now clear that it does not require immune effector cells. Interestingly, SFs may also be able to dampen the immune response via the production of transforming growth factor- β , soluble tumour necrosis factor receptors and interleukin-10, as well as extracellular matrix degradation by tissue inhibitor of metalloproteinases. In an analogous fashion to regulatory T cells, this seeming paradox may in fact reflect the presence of different populations of regulatory SFs present in a RA joint that are yet to be defined. Recent data also provide another intriguing role for the SFs, which are clearly producing factors supporting angiogenesis such as transforming growth factor- β , platelet derived growth factor, granulocyte macrophage colony stimulating factor, epidermal growth factor, vascular endothelial growth factor and fibroblast growth factor. Since angiogenic support is a distinctive property of cancer cells, it provides support for the older speculation that RA SFs could in fact be malignant cells, which is now further supported by the recent demonstration that angiogenesis inhibitors are able to ameliorate arthritis development in a mouse model.

The potential of RA SFs to behave as transformed cells is also documented by their expression of intracellular products able to modulate the cell cycle. For example, as discussed in the fourth review [4], the levels and activation patterns of AP-1 and p53 gene products may, at least in part, be responsible for the aggressive, proliferative and cartilage attacking properties of RA SFs. In support of the malignancy hypothesis is the notion that synovial hyperplasia results from increased proliferation of RA SFs either spontaneously or in response to cytokines, with the increased expression of c-myc, c-jun and nuclear factor κ B factors indicating that hyperproliferation may indeed occur. However, although this appears to be a widely accepted property of RA SFs in culture, it is not clear if proliferation occurs *in vivo*. An alternative explanation to hyperproliferation is defective apoptosis. Apoptotic signals provided by molecules such as PTEN, c-myc, p16 and SENTRIN have been reported as reduced in RA SFs, and these cells show reduced apoptosis *in situ*. Resistance to apoptosis may also result from desensitization of both Fas

and tumour necrosis factor receptor pathways. The upregulation of transcription factor complexes such as nuclear factor κ B and AP-1 indicate increased transcriptional activities in RA SFs. Interestingly, most of the disease-associated products like cytokines and matrix metalloproteinases are controlled by these transcription factors. It is logical, although still speculative, to assume that mutations/events leading to distorted signalling from these modules may result in altered cytokine patterns and effector responses by SFs.

It is clear that the field of synovial fibroblast research is still in its infancy. Although there is sufficient information to support the role of SFs as a major contributor to joint degradation, their functional role in modulating the pathogenic inflammatory and autoimmune responses in RA joints remains poorly defined. Are SFs capable of initiating the arthritic reactions or is their role merely supportive? How do these cells affect macrophage activation and homing? Can they also affect local lymphocyte responses, and what may be the outcome? Is the SF response multi-clonal or monoclonal? Are there distinct functions in the different types of SFs and can we hope that regulatory SFs may exist?

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