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REVIEW ARTICLE

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Interactions between T cells and synovial fibroblasts

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Abstract T lymphocytes, synovial macrophages, and synovial fibroblasts are the three most abundant cell populations in rheumatoid arthritis synovial tissue, and each is believed to play an important role in the pathogenesis of joint inflammation and destruction. While interactions between T cells and macrophages and between macrophages and fibroblasts have been carefully studied, less attention has been paid to potential interactions between T lymphocytes and synovial fibroblasts. In this review we consider available data which suggests that cell–cell contact between T lymphocytes and synovial fibroblasts may lead to activation of each cell type. This interaction is likely to be significant in the pathophysiology of rheumatoid arthritis.

Introduction

The role of T lymphocytes in the pathogenesis of rheumatoid arthritis (RA) remains controversial.[1] At the same time, there has been growing appreciation of the role of type B (fibroblastic) synoviocytes in the erosion of cartilage and bone that is the hallmark of tissue destruction and the development of deformities in patients with RA.[2] These synoviocytes exhibit a phenotype that, in some respects, resembles transformed or partially transformed cells. Their enhanced growth potential in vivo mirrors the hyperplasia of type B synoviocytes seen in vivo. Both in vivo and in vitro, these cells secrete a range of inflammatory mediators, including the cytokines IL-6 and IL-8, prostaglandins, including PGE2, and matrix metalloproteases (MMPs) such as stromelysin. Monocyte-derived cytokines such as IL-1 and TNFα are known to be capable of activating expression of these inflammatory mediators by synoviocytes. Thus, in one view, interactions between type A (macrophage-like) synoviocytes and type B (fibroblastic) synoviocytes can explain most, if not all, of the key elements of chronic RA, without invoking a central role for T cells.[2]

In this view of RA, T cell–monocyte interactions could still be important as a means of monocyte activation. However, a direct interaction between T cells and synovial fibroblasts has not typically been viewed as a component of the pathogenesis of RA, although the capability of these cells to bind to each other has been known for over 10 years.[3]

In this present review, the focus will be primarily on studies of interactions between T cells and synovial fibroblasts in RA synovium, and will emphasize recent observations. Consideration of these issues is not only of importance in understanding RA, but should also bear upon appropriate directions for innovations in its therapy.

Cytokine-mediated interactions in RA synovium

Cytokines play a dominant role in the pathophysiology of joint inflammation and destruction in RA.[4,5] The central roles of TNFα and IL-1β have been well documented. Levels of T cell-derived cytokines, such as IL-2, tend to be low, and this has cast doubt on the role of T cells in RA.

Some recent findings concerning cytokines present in the synovial compartment have, however, partially answered some of the apparent paradoxes regarding a possible role for T cells. Thus, IL-12 has been found in the synovial compartment,[6] and is known to be a key cytokine in the differentiation of Th1 cells, which appear to be the primary CD4 T cell subset in RA synovium. The recently discovered cytokine IL-15, which has IL-2-like activities, is also present in RA synovium,[7] and may be more important than IL-2 as a T cell growth factor in these lesions. Finally, IL-17, a cytokine produced by activated T cells that can stimulate fibroblasts, has also been found in RA synovium.[8] These

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findings suggest that T cell interactions with other cell types in the joint may indeed be important in the pathogenesis of RA. If polyclonal T cell activation mechanisms, driven in part by cytokines, are a significant factor in RA synovium, then the lack of a reproducible pattern of T cell clonality, repertoire usage, and antigen-specific response may not rule out an important role for polyclonal T cell populations in the generation and maintenance of chronic synovitis.

Cell–cell interactions in RA synovium

Distinct cell populations in synovium that can interact with T cells include type A (macrophage-like) synoviocytes, type B (fibroblastic) synoviocytes, dendritic cells, and B lymphocytes. Current understanding of synovial fibroblast function emphasizes its role in the destruction of cartilage and bone.[2] However, these cells can also support survival and differentiation of B lymphocytes.[9] Recent data also suggests that the cell types which might serve as antigen-presenting cells (APC) or accessory cells for T cell activation include not only the "professional APC" that are bone marrow derived, but also the synovial fibroblasts.[10–12]

The interaction of monocytes/macrophages with fibroblast-like cells in the rheumatoid synovium has been well documented, but less is known about T cell interactions with synovial fibroblasts. The interaction of activated T cells with synovial fibroblast-like cells results in the accumulation of TNF-α, interferon-gamma (γ-IFN), and IL-6. Furthermore, the T cell–synoviocyte interaction up-regulates expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on synovial fibroblasts. Both cytokine accumulation and adhesion molecule expression are dependent on cell contact between T cells and synoviocytes.[13]

Membranes of stimulated T cells also induce the production of PGE2 and MMP-1 by synoviocytes.[14,15] Blocking experiments using monoclonal antibodies and cytokine antagonists indicate that T cell membrane-associated IL-1 and TNF, but not CD69, CD40 ligand, or CD11b, were involved in the induction of MMP-1 and PGE2 production. These results demonstrate that activated T cells may directly affect synoviocyte function.[14,15] Activated T cells were also found to induce IL-1β production by an SV-40 virus-transformed synovial fibroblast line, in part through CD11a/CD18 mediated intercellular adhesion.[16]

Bidirectional interaction of resting T cells and synovial fibroblasts

Recent findings in our laboratory may also point to a new role for synovial T cells, in direct interaction with type B (fibroblastic) synoviocytes.[17] In earlier studies, we, and others,[10–12] found that synovial fibroblasts could serve as surprisingly potent accessory cells for T cell activation by superantigen or lectin, but not by anti-CD3.

Activation of T cells in these experiments involves cell–cell contact (Fig. 1), and was blocked by antibodies against CD2, CD11a/CD18 (lymphocyte function-associated antigen 1; LFA-1), and Class II MHC. Antibody to Class II MHC also blocked T cell activation in experiments in which synoviocytes were not pretreated with γ-IFN and did not express Class II MHC at levels detectable by flow cytometry.[11] This suggests that a very small number of MHC molecules can successfully present superantigens to T cells in this system, and/or that Class II MHC might be induced on synoviocytes following interaction with T cells.

In more recent experiments, we have begun to explore the potential activation of synoviocytes in this system.[17] Initial experiments showed that synoviocyte activation was induced by the combination of T cells and superantigen. Previous work of others had shown that high concentrations of superantigen could activate type B synoviocytes,[18,19] and we found that this was also true for bacterial superantigens in the ng/ml concentration range.[17] Interestingly, control

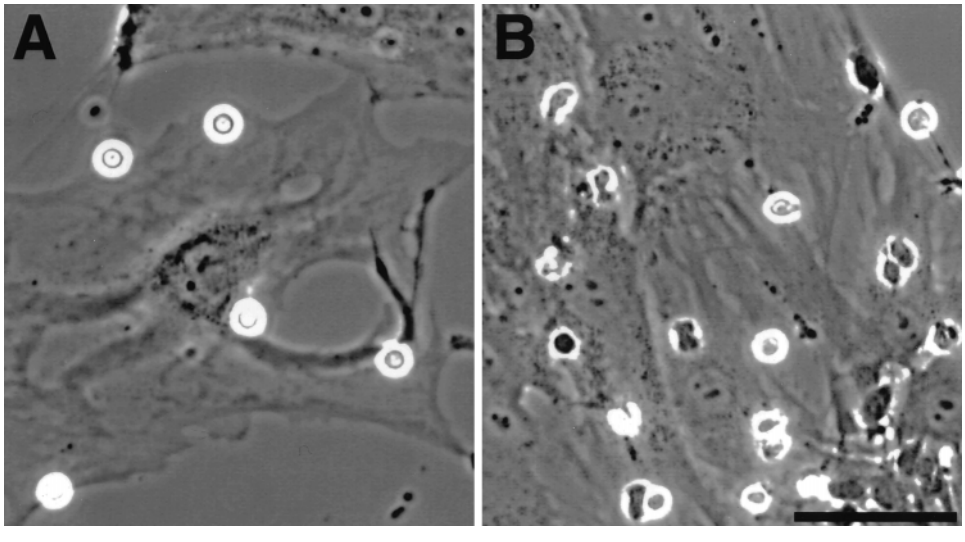

Fig. 1. Interaction between T cells and synovial fibroblasts: morphological differences between unactivated and activated T lymphocytes in co-culture with fibroblast-like synoviocytes. **A** Unactivated T cells found on top of cultured fibroblast-like synoviocytes are round when viewed with phase-contrast optics. **B** In contrast, when T lymphocytes and fibroblast-like synoviocytes are cultured for 24 h in the presence of superantigen (staphylococcal enterotoxin A – 10 ng/ml), many T lymphocytes are phase-dark and display an ameoboid morphology. Bar = 40 μm

Table 1. Synovial fibroblast stimulation by resting T cells

1. Does not require T cell activation
2. Leads to expression of IL-6, IL-8, stromelysin, and PGE2
3. Synergizes with IL-17
4. Is induced by different types of T cell subsets

cultures containing resting T cells and synoviocytes but no superantigen also gave evidence of synoviocyte activation (Table 1). Resting T cells synergized with low concentrations of IL-17 that had no effect on fibroblast function on their own.[17] Purified CD4+ or CD8+ subsets, and memory or naïve subsets (CD45RO+ or CD45RA+), were equally able to stimulate fibroblast gene expression.[17] The T cells did not become activated during this interaction, and did not express mRNA for IL-2.[17]

Conclusion

It is becoming clear that multiple cell types, other than differentiated cells of the immune system, can participate in immunologic responses, both physiologic and pathologic. In inflamed synovial tissue, one example would be antigen presentation to T cells by synovial fibroblasts. Since synovial fibroblasts generally lack ligands for CD28,[11] a major receptor on the T cell membrane for co-stimulatory signals, the pathway of T cell differentiation that results from such interactions could differ from events that follow stimulation of T cells by professional APC.

A new and surprising observation is that resting T cells, in the absence of CD3-TCR triggering, possess significant effector functions. This is revealed by the activation of various genes in synovial fibroblasts, encoding for pro-inflammatory molecules, after contact with resting T cells or T cell subsets. This implies that the presence of polyclonal T cells, resting and/or activated in certain tissues, could have a pro-inflammatory effect, even in the absence of recognition of autoantigens or exogenous antigens.

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