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Synovial biology and T cells in rheumatoid arthritis

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Abstract

Events that occur in rheumatoid arthritis synovial tissues are responsible for the signs and symptoms of joint inflammation and for the eventual destruction of articular and periarticular structures that lead to joint dysfunction and disability. The three most abundant cell populations in RA synovium are synovial macrophages (type A synoviocytes), synovial fibroblasts (type B synoviocytes) and infiltrating T lymphocytes. Other important cell populations include B lymphocytes, dendritic cells, plasma cells, mast cells and osteoclasts. Our current understanding of rheumatoid arthritis is moving beyond previous concepts that view this disease as the consequence of a specific and focused humoral or cellular autoimmune response to a single autoantigen. Rather, a new view of rheumatoid arthritis is emerging, which seeks to understand this disease as the product of pathologic cell–cell interactions occurring within a unique and defined environment, the synovium. T lymphocytes in rheumatoid arthritis synovium interact closely with dendritic cells, the most potent antigen-presenting cell population in the immune system. T cells also interact with monocytes and macrophages and cytokine-activated T cells may be, especially, suited to trigger production of the important cytokine TNFα by synovial macrophages. Recent evidence also suggests a potent bidirectional interaction between synovial T cells and synovial fibroblasts, which can lead to activation of both cell types. An important role for synovial B lymphocytes has been emphasized recently, both by experimental data and by results of clinical interventions. B cells in synovium can interact with fibroblasts as well as with other cells of the immune system and their potential role as antigen-presenting cells in the joint is as yet underexplored. Rheumatoid arthritis synovium may be one of the most striking examples of pathologic, organ-specific interactions between immune system cells and resident tissue cell populations. This view of rheumatoid arthritis also leads to the prediction that novel approaches to treatment will more logically target the intercellular communication systems that maintain such interactions, rather than attempt to ablate a single cell population.

Keywords: T cells; B cells; Fibroblasts; Dendritic cells; Monocytes

1. Introduction

The hallmark lesion of rheumatoid arthritis (RA) is synovial inflammation—synovitis—that leads to erosion and destruction of cartilage, bone and periarticular structures. While the etiology of RA remains unknown and controversy persists concerning the role of humoral and cellular autoimmunity in the pathogenesis of RA, substantial insight has been achieved into the processes and molecular mediators that characterize the synovial biology of RA. RA synovium contains a variety of cell types many of which are listed in Table 1. No single cell population is capable of causing RA, although aggressive fibroblasts from RA pannus possess autonomous tissue invasive properties, even after extraction from established synovial lesions. It has become increasingly clear that interactions among the important cell populations in the RA synovium not only define many aspects of the synovial biology of this disease, but also offer targets for therapeutic interventions.

Interactions between cell populations in RA synovium can be thought of as falling into two classes: first, interactions mediated by secreted molecules, such as cytokines and second, cognate cell–cell interactions that require direct contact between two different types of cells and that alter the activation or differentiation state of one or both of the cell types. Some of these interactions that are relevant to the pathogenesis of RA are listed in Table 2. This review will focus on interactions between lymphocytes in RA synovium and the other key cell populations, such as dendritic cells, monocyte-macrophage cells and synovial fibroblasts and will emphasize recent findings.

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Table 1
Cellular components of the rheumatoid synovium

Abundant cell populations
• T lymphocytes
• Macrophage-like (type A) synoviocytes
• Fibroblastic (type B) synoviocytes
Other cell populations
• Dendritic cells
• B lymphocytes
• Plasma cells
• Mast cells
• Osteoclasts

Table 2
Cell–cell interactions in rheumatoid arthritis synovium

• Leukocyte–endothelial
• T cell–antigen-presenting cell
• Macrophage–fibroblast
• T cell–fibroblast
• B cell–fibroblast

2. Interactions between synovial dendritic and T cells

Dendritic cells are, especially, powerful initiators of immune responses, even when present in small numbers. In RA, dendritic cells are actually abundant both in synovial tissue and in synovial fluid. Attention, therefore, has been directed at possible roles of dendritic cells in initiation and perpetuation of rheumatoid synovitis (recently reviewed in Ref. [1]). Cells with dendritic morphology were initially recognized in RA synovial tissue over 2 decades ago. Key observations were made in 1982 by Klareskog et al. who proposed that RA synovitis was a delayed-type hypersensitivity reaction generated by the interaction of synovial dendritic and T lymphocytes [2]. These dendritic cells, which were noted to be functionally similar to Langerhan cells of the skin, were partially purified and were shown to be powerful immune stimulators.

Subsequently, such cells were also found in synovial fluid, comprising as many as 5% or more of RA synovial fluid mononuclear cells. Synovial fluid dendritic cells were capable of attracting a cluster of T lymphocytes and activating antigen-specific T cell responses. In synovial tissue, dendritic cells were found within both large and small lymphoid aggregates adjacent to vascular structures. These cells express a variety of co-stimulatory ligands known to be important in interactions with T lymphocytes.

Dendritic cells have been proposed to be critical for the development of the architecture of inflamed RA synovium, which can vary from an appearance similar to a lymph node to a diffuse lymphocytic infiltrate. The entry of dendritic cells and their positioning within synovial tissue may be dependent on specific chemokines, such as CXCL12. This chemokine binds to the receptor CXCR4 and both are highly expressed in perivascular and sublining regions of RA synovium.

Secretion of cytokines by dendritic cells can skew the nature of the T cell immune response. Th1-inducing cytokines include IL-12, IL-23 and IL-27. IL-23, discovered recently, may be of particular importance because of its ability to induce expression of IL-17, a T cell cytokine capable of activating synovial fibroblasts to express pro-inflammatory and tissue-destructive mediators. Dendritic cells are also one of the sources of IL-1, IL-6 and TNFα, important pro-inflammatory cytokines that are targets of biologic therapeutic agents in RA.

A critical question is the nature of the autoantigens or foreign antigens to which the immune response is directed and focused in RA. A wide variety of such antigens are known to be capable of preferentially stimulating T cells, especially, synovial compartment T cells in RA. The association of RA with the HLA-DR4(0401) Class II MHC allele has raised the possibility that specific MHC molecules present arthritogenic antigens and initiate or perpetuate RA. However, a variety of other mechanisms to explain the association of RA with MHC alleles have been proposed and none has yet been proven. Whichever antigens turn out to be most important, it is likely that dendritic cells are the most critical antigen-presenting cell population involved in initiating these responses. An, especially, intriguing issue is the location of such responses: does RA begin in the joints or begin systemically with immune responses triggered by events in other tissues?

3. Monocyte activation by T cells in RA

Infiltrating T cells and macrophages reside in close proximity in the inflamed RA synovium. This intimate association provides many opportunities for interactions between the cells [3,4]. Evidence supporting T cell participation in TNFα production comes from experiments in which depletion of CD3+ cells from RA synovial cell cultures resulted in decreased TNFα production, whereas depletion of CD3+ cells from OA cultures did not [5]. These observations suggest that T cells have a direct impact on TNFα induction in RA joints. To further investigate the role of T cells in TNFα production, T cells activated by a cytokine cocktail (Tck) [6] were used, as a model for RA T cells, to stimulate monocytes. Tck were able to induce TNFα from monocytes via a cell–cell contact-dependent mechanism that mimicked RA T cells, but differed from T cells activated through their TCR and CD28 [5]. Another study indicates that Tck can also induce production of the anti-inflammatory cytokine IL-10 by M-CSF-treated monocytes (i.e. macrophages) [7]. These studies imply that RA synovial T cells are similar to bystander-activated Tck in their phenotype and their effects on monocyte/macrophage cytokine production.

The receptor activator of nuclear factor κB ligand (RANKL) has been detected in RA synovial tissue. RANK/RANKL interactions are necessary for the differentiation of osteoclasts from monocytic precursor cells. RANKL was found to localize specifically to CD3+ CD4+ cells and not other mononuclear cells, in synovial histological sections [8].