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Review

The Role of T Cells in Rheumatoid Arthritis

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Abstract. In rheumatoid arthritis (RA), T cells infiltrate into the synovial membrane where they initiate and maintain activation of macrophages and synovial fibroblasts, transforming them into tissue-destructive effector cells. The diversity of the disease process and the formation of complex lymphoid microstructures indicate that multiple T cell activation pathways are involved. This model is supported by the association of distinct disease patterns with different variants and combinations of HLA class II molecules. T cell pathology in RA, however, is not limited to the joint. Affected patients have major abnormalities in the T cell pool, with a marked contraction in T cell receptor diversity and an outgrowth of large clonal populations. Clonally expanded $CD4^+$ T cells lose expression of the CD28 molecule and gain expression of perforin and granzyme. Consequently, the functional profile of expanded $CD4^+CD28^{null}$ T cells is fundamentally changed and is shifted towards tissue-injurious capabilities. $CD4^+CD28^{null}$ T cells are particularly important in patients with extra-articular manifestations of RA, where they may have a direct role in vascular injury. Understanding the mechanisms underlying the loss of T cell diversity and the emergence of pro-inflammatory $CD4^+CD28^{null}$ T cell clonotypes may have implications for other autoimmune syndromes.

Key words: HLA; autoimmunity; cytokines; synovitis; oligoclonality; $CD4^+CD28^{null}$.

Rheumatoid arthritis (RA) is a crippling disease that predominantly affects individuals in the prime of their lives. In early disease, pain and stiffness are the major manifestations, but, eventually, irreversible damage of joints, tendons and bones develops. The underlying lesion is a destructive inflammatory tissue composed of two components, infiltrating T cells and macrophages and resident synovial membrane cells, both of which play a part in the tissue damage[9]. Stimulated macrophages produce inflammatory cytokines and metalloproteinases that directly damage the tissue and, in response to immune stimulation, synovial fibroblasts undergo profound phenotypic and functional changes and acquire the ability to erode and invade into cartilage and bone.

The prognosis of patients with RA is determined to some extent by the aggressiveness of the synovial lesion, but more so by the development of extra-articular rheumatoid disease[20, 28, 29]. Extra-articular RA can manifest in almost every organ system, emphasizing the systemic nature of the syndrome. It has been proposed that rheumatoid disease of the joint and of non-articular organs represent two, partially independent dimensions of RA[42, 45]. This concept has been suggested by the observation that genetic risk factors are particularly important for just one aspect of RA. The emerging model predicts that a shared risk factor exists that predisposes a person to both articular and extra-articular RA; additional risk determinants guide the disease towards one that involves predominantly joint inflammation or one characterized by extra-articular manifestations[41].

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The traditional paradigm for the pathogenesis of RA assumes that the disease process is ultimately driven by antigen-specific T cells that recognize arthritogenic antigen and maintain the chronic inflammatory response[39]. Although simplistic, this model has been very productive in guiding the investigation of RA. However, this paradigm has recently been challenged because it cannot account for many of the findings in affected patients. In this review, an attempt has been made to summarize recent data on T cell physiology in RA and to integrate these data into a new model of RA pathogenesis.

Disease-Risk Genes and T Cell Function in RA

Support for a central role of T cells in RA pathogenesis comes from the demonstration that the strongest genetic risk for RA is conferred by the HLA locus[27]. Indirect evidence from multiple lines of research supports the contention that the HLA-DRB1 locus has a direct involvement in the disease process[7, 41]. In most ethnic groups and in most geographic regions around the world, HLA-DRB1 genes are nonrandomly distributed in patients with RA. HLA-DRB1*01 and *04 alleles are consistently over-represented and it has been hypothesized that the biologic effect is introduced by a defined sequence motif in amino acid positions 70-74[48]. The possible involvement of polymorphic sites on HLA class II molecules has been interpreted as evidence that antigen selection and presentation are critical in RA. Accumulated data, however, question that the only function of RA-associated HLA-DRB1 molecules is peptide selection. In fact, there is increasing evidence that HLA-DR polymorphisms may not be central in disease initiation, considered to be the ultimate event in a pathological T cell response leading to RA. Not predicted by the peptide selection model, disease-associated HLA-DRB1 alleles differ in their potency to confer risk. HLA-DRB1*0401 has consistently been found to confer the highest degree of susceptibility[6, 44]. Alleles with a similar yet not identical sequence in the third hypervariable region of the HLA-DRB1 chain have been identified as the primary risk alleles for seronegative RA, a less aggressive disease variant[46]. Also, a gene-dose effect for HLA-DR alleles has been demonstrated in RA. Affected patients often inherit not only one, but frequently have two RA-risk genes[38, 44]. Allelic combinations have been associated with variations in disease severity, supporting the conclusion that HLA--DRB1 molecules function as progression factors and disease modulators instead of being involved in disease initiation.

The over-representation of RA-associated HLA-DRB1 alleles on both haplotypes has led to the proposal that MHC class II molecules influence RA pathogenesis primarily by selecting the T cell repertoire and not by presenting arthritogenic antigens[8, 40, 41]. Experimental data confirm that the composition of the T cell receptor repertoire has a disease-specific fingerprint that is altered in individuals with RA when compared with age--matched healthy donors[35].

Studies of HLA class II molecules in RA have been helpful in dissecting the phenotypic heterogeneity of the disease[43, 45]. Preferential expression of defined HLA-DR alleles in patient subsets with specific clinical characteristics has brought recognition that RA is a heterogeneous syndrome encompassing multiple different subtypes. MHC class II genotypes are currently being studied as biomarkers to separate RA phenotypes. The association of different HLA-DRB1 genes with distinct types of RA indicates that the contribution of HLA molecules in RA pathogenesis is complex and not limited to a single pathway.

T Cells in the Synovial Lesion

Tissue-eroding infiltrates in the synovial membrane are composed of T cells, B cells, macrophages, dendritic cells and synoviocytes. T cell dependence of the inflammatory reaction has been inferred from experiments that suggest antigen-specific activation of lesion T cells[3, 14], including *in situ* proliferation and clonal expansion of identical T cell receptors in distinct joints (Table 1)[11, 15, 23]. Proof for the ultimate regulatory role of T cells in synovitis comes from T cell depletion experiments[13]. T cells were eliminated from the synovial tissue and the function of surviving cells was evaluated. These experiments were made possible by a novel "animal model" of RA. Synovial tissue from RA patients was implanted into severe combined immunodeficiency (SCID) mice to create synovium-SCID mouse chimeras. In the grafts, the disease process was well maintained, as determined by the ongoing production of the

Table 1. T cells in the synovial lesions

Evidence for T cell involvement in RA
Dominant population of tissue-infiltrating cells
Undergo clonal expansion in the tissue
Representation of identical T cell clones in different sites
Provide help in the formation of lymphoid microstructures
Disruption of synovitis following T cell depletion

proinflammatory cytokines, IL-1, TNF-α, IL-6, IL-2 and IFN-γ. Also, the metalloproteinases, MMP-1 and MMP-3, were abundant in the engrafted tissue. Depletion of synovial T cells by treating the chimeras with anti-CD2 antibodies resulted in a prompt cessation of tissue IFN-γ production, followed by a sharp decline in the *in situ* production of IL-1α, TNF-α, MMP-1, and MMP-3. Also, the T cell growth factor IL-15, suspected to amplify T cell activation in the inflamed joint, was lost after the elimination of T cells. A critical role of the T cell product IFN-γ in regulating synovitis was demonstrated by reconstituting the synovium-SCID mouse chimeras with recombinant IFN-γ after they had received the T cell-depleting antibody treatment. Exogenous IFN-γ completely restored the production of proinflammatory monokines and tissue-digesting metalloproteinases.

Additional clues of the involvement of T cells in rheumatoid synovitis have come from studies of the lymphoid microstructures formed by tissue-invading lymphocytes (Table 2). Synovial infiltrates display discrete patterns, defining several subtypes of rheumatoid disease[12]: T cells, B cells and macrophages can be diffusely dispersed throughout the synovial membrane; T cells and B cells can be arranged in clusters that can generate fully developed germinal center reactions; or the synovitis can be characterized by granuloma formation. Germinal centers and granulomas are sophisticated microstructures that depend on T cell help. A particular CD8 T cell subset expressing CD40-ligand has been implicated in germinal center formation[34]. A critical issue that remains is to determine whether the distinct types of synovitis reflect different causative antigens or derive from differences in the host response pattern to identical antigens.

Table 2. Multiple pathways of T cell activity in RA synovitis

T cells in follicular synovitis
Interact with B cells
Interact with interdigitating dendritic cells
Provide help for germinal center reactions
$CD8^+$CD40-ligand$^+$ T cells surround follicles
T cells in granulomatous synovitis
Interact with macrophages
Produce large amounts of IFN-γ
T cells in diffuse synovitis
Produce small amounts of IFN-γ
Do not form lymphoid microstructures

T Cell Abnormalities and Extra-Articular Disease

RA patients have fundamental abnormalities in T cell function that are not restricted to the T cells participating in the synovial infiltrates. One aberration is the expansion of selected CD4 T cells to large clonal populations[25, 26]. CD4 oligoclonality is most predictably encountered in patients with extra-articular disease[18, 32].

Extra-articular manifestations of RA shorten the life expectancy of the patient, attributable to cardiovascular complications. Vasculopathy in RA may take one of several forms, spanning from frank arteritis to accelerated atherosclerosis. Available data strongly suggest that vascular injury may be mediated by a unique T cell subset, the $CD4^+CD28^{null}$ T cells. CD28-deficient T cells were initially identified when clonally expanded populations from patients with severe RA were characterized[5]. $CD4^+CD28^{null}$ T cells are a specialized subset of T cells, distinct from classical CD4 T cells (Table 3). $CD4^+CD28^{null}$ T cells produce large amounts of IFN-γ, even in the absence of costimulatory signals[22]. They persist over many years[32], possibly due to a defect in clonal down-sizing[24]. Molecular characterization of these cells has demonstrated that defective transcription of the CD28 gene is related to the loss of two nuclear factors functioning as transcription initiation proteins[30, 31]. While deficient for these nuclear factors, $CD28^{null}$ T cells have gained expression of several other molecules, including perforin and granzyme B[21]. As a consequence, their functional profile is changed and they can function as cytotoxic effector cells[37]. It may be this cytotoxic potential that equips these cells to mediate endothelial injury and the vascular damage common in the extra-articular manifestations of RA. Support for a direct role of $CD4^+CD28^{null}$ T cells in vascular disease has come from studies describing the accumulation of $CD4^+CD28^{null}$ T cells in patients with acute coronary syndromes[17]. Clonally expanded $CD4^+CD28^{null}$ T cells have been isolated from the ruptured atherosclerotic plaque of patients with fatal myocardial infarction[16].

Table 3. Comparison of $CD4^+CD28^+$ and $CD4^+CD28^{null}$ T cell subsets

Activity	$CD4^+CD28^+$ T cell	$CD4^+CD28^{null}$ T cell
Expression of α-β T cell receptor	+	+
Utilization of CD80/CD86	+	–
Expression of CD40-ligand	+	–
Production of large amounts of IFN-γ	(+)	+
Expression of perforin/granzyme B	–	+
Expansion to large clonal populations	–	+
Impaired apoptosis/clonal downsizing	–	+
Autoreactivity	–	+

The clonal outgrowth of $CD4^+CD28^{null}$ T cells breaks a principal rule of T cell physiology and raises the question of how selected T cell specificities can gain a survival advantage. Different mechanisms could apply, ranging from antigen-driven proliferation to defects in T cell down-sizing. A recent study of patients with RA has posed yet another possibility. Using random T cell receptor α-chain picking and limiting dilution analysis, frequencies for individual CD4 T cells have been estimated in the total T cell compartment. Frequencies of CD4 T cells using either a BV8 or BV5 gene segment for T cell receptor rearrangement were more than ten-fold higher in RA patients than in age-matched controls[33], suggesting that RA is associated with a marked contraction of the T cell receptor repertoire. In a contracted repertoire, some T cell specificities may reach sufficient size to be detected as frank clonal expansions. The frequency distribution of T cell receptor α-chains from RA patients, however, has indicated that the vast majority of CD4 T cells must have undergone proliferation, in most cases insufficient to appear as a clonally expanded population. In conclusion, $CD4^+CD28^{null}$ T cells that proliferate into large clonal populations in RA may represent just the tip of the iceberg in a T cell compartment characterized by oligoclonal T cell proliferation.

One of the intriguing questions that has developed from the data is the relationship between the loss of T cell diversity and autoimmune inflammatory disease. It could be argued that T cell repertoire contraction is a consequence of disease. Available data do not support this notion. Contraction in T cell diversity was found in patients very early in the disease, with no indication that persistent disease was associated with progressive loss of diversity[33]. Also, lessons learned from experimental therapy in RA patients favor a primary deficiency in T cell homeostasis. Supported by the idea that RA is a sequela of antigen-specific T cell activation in the joint, therapeutic approaches were developed in the early 1990's to eliminate peripheral T cells in patients to open a window of opportunity for a repopulating pool with novel, non-disease-involved T cells. Antibody-mediated T cell depletion was successfully achieved in patients who received the monoclonal antibody Campath-1H, directed against the T cell and B cell antigen CD52[2]. Early after treatment, inflammatory scores dropped, but patients had reactivation of synovial inflammation while still experiencing profound peripheral lymphopenia[19, 36]. More importantly, the peripheral repertoire of CD4 T cells was massively contracted and dominant clonal T cell populations were shared between persistent synovial lesions and the peripheral pool[4, 10]. Thus, polyarthritis can persist in the setting of lymphopenia and only a small population of CD4 T cells is required to sustain synovitis. The most important information from these trials was that RA patients had marked difficulties in repopulating the T cell compartment. Peripheral CD4 T cell counts remained depressed to lymphopenic levels for an extended period, raising the interesting question whether RA patients have fundamental difficulties in generating and maintaining a diverse T cell compartment.

A New Model for RA: Synovitis as a Consequence of a Contracted and Autoreactive T Cell Repertoire

The simplicity of the traditional paradigm, which considers RA as a disease caused by the recognition of a self antigen in the joint, has been appealing. The formulation of a new pathogenic model, however, has been necessitated by data that challenge such a simplistic view. Two major developments have shaped the emergence of the new pathogenic model. RA is now recognized as a heterogeneous syndrome. There is a diversity of disease patterns occurring in different patients. Enrichment of certain HLA-DRB1 alleles and their combinations have been associated with defined variants of disease. Sex genes have been implicated as disease modulators in population-based studies that have demonstrated male and female disease patterns of RA[1, 47]. Involvement of T cells in determining not only the onset but, more importantly, the evolution of the rheumatoid syndrome is indicated by the formation of lymphoid microstructures in the inflamed joint. Distinct T cell functions are relevant in the generation of granulomas, germinal centers or diffuse dispersed infiltrates (Table 2). More than one T cell activation pathway and more than one functional T cell subset must be involved in RA pathogenesis. Considering the heterogeneity of the disease process, it could be proposed that not one but multiple disease-causative antigens are relevant and that the primary defect leading to disease lies in the inability of the host immune system to maintain tolerance, not in the selective expansion of a few antigen-specific cells.

A novel view of autoimmunity in RA is encouraged by the finding that T cell pathology is systemic and is not limited to the joint (Fig. 1). While the perception that RA is a systemic disease fits well with clinical experience, it requires a rethinking of the simple model that tolerance is lost towards a small set of joint antigens. Rheumatoid arthritis can manifest in the lungs,

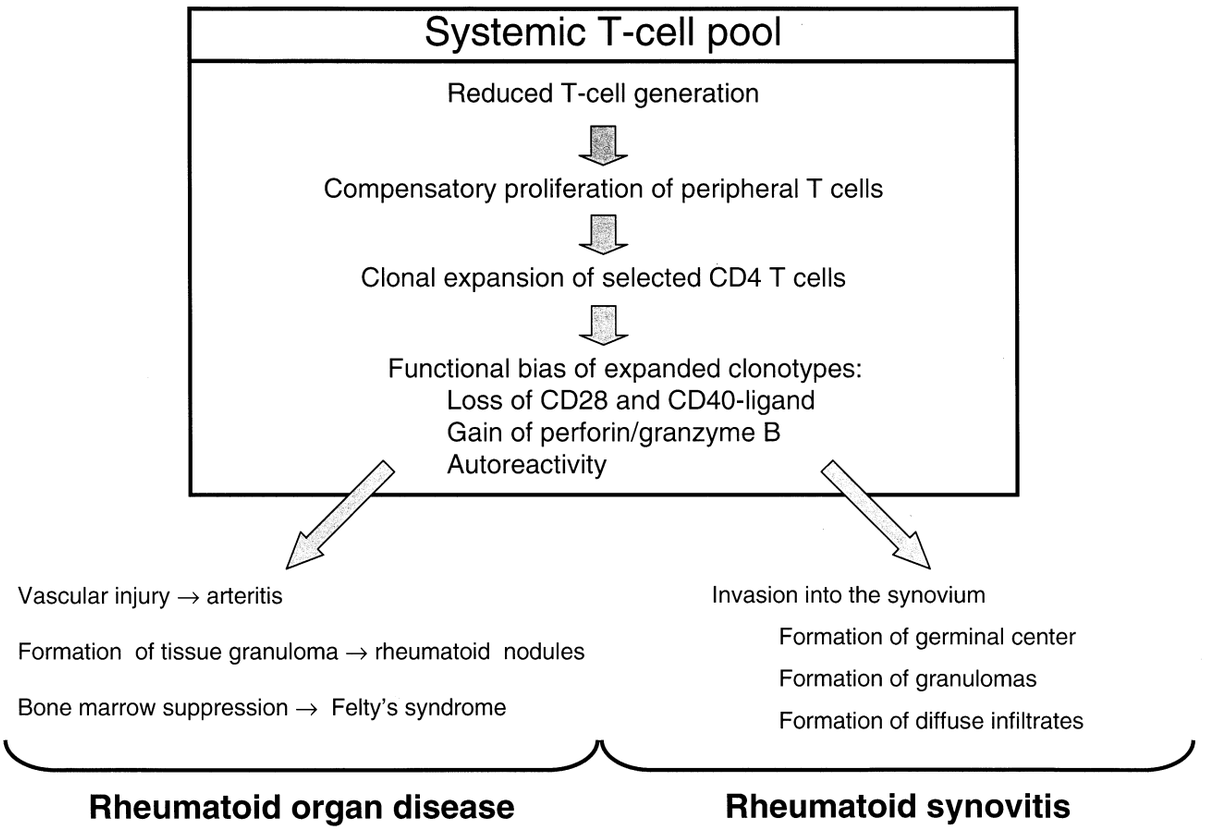

Fig. 1. Hypothetical disease model for rheumatoid arthritis. At the core of rheumatoid arthritis is most likely a defect in the systemic T cell pool that leads to a clonal expansion and functional differentiation of $CD4^{+}CD28^{null}$ T cells. These cells are then able to act systemically or invade the joint, which leads to rheumatoid organ disease or rheumatoid synovitis, respectively

the peripheral nerves, the heart and the blood vessels, creating life-threatening complications. Only a subset of patients will experience extra-articular disease, suggesting that additional genetic risk factors are necessary to superimpose nonarticular disease on synovitis. Recent findings of abnormalities in T cell homeostasis provide an opportunity to account for system-wide disease (Fig. 1). In patients with RA, the T cell pool is sharply contracted in diversity, possibly reflecting the inability to produce sufficient numbers of T cells. A defect in T cell generation would lead to clonal expansion of peripheral T cells in an attempt to fill the void. Because the dilution of autoreactive T cells may be one mechanism of maintaining tolerance, the risk of self-recognition probably increases with increasing size of individual clones. A shift of a contracted repertoire towards autoreactivity may result from other processes as well. Recognition of self-HLA-antigen complexes is possibly involved in regulating T cell survival and turnover. Replicative stress to maintain the size of the T cell compartment would increase the likelihood of anti-self-reactive T cells to emerge. Finally, it has to be considered that a higher number of self-reactive T cells could escape negative selection as the demand of the system for replenishment is increased. Experimental evidence indicates that $CD4^{+}CD28^{null}$ T cell clones isolated from RA patients are responsive to self antigens[25]. Their mere size could amplify their potential to cause ongoing autoimmune disease. Data have also been provided that the repertoire of naive, antigen-inexperienced T cells is biased in RA patients and that lesional T cells in the synovial infiltrates derive from T cells over-represented in the naive repertoire[49].

Why would the immune system choose the synovial membrane to display its self-reactive potential? Immune responses are not solely determined by the presence of antigen-specific precursors. Clustering of cells in time and space, surpassing of a critical mass, and signals derived from the microenvironment are all involved in making it possible for multicellular reactions to occur. Undoubtedly, the synovial microenvironment is unique and may provide necessary elements

favoring the occurrence of immune reactions. Understanding the unique ingredients the joint provides may let us redirect immune responses away from the synovium. Understanding the diversity of the T cell population and stimulation pathways in RA may allow us to disrupt the inflammation with approaches that are tailored to each patient. Understanding the precise relationship between T cell homeostasis, T cell repopulation dynamics and autoreactivity may give insights that reach far beyond rheumatoid arthritis.

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