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REVIEW

THE ROLE OF T CELLS IN THE IMMUNOPATHOGENESIS OF RHEUMATOID ARTHRITIS

New Perspectives

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Introduction

Consideration of the possibility that T lymphocytes might be central to the pathogenesis of rheumatoid arthritis (RA) first became prominent in the 1980s (1). Only after new approaches became available for understanding the physiology of the T lymphocyte, particularly the generation of monoclonal antibodies that identified the function of important T cell surface structures, was there the development of a hypothesis for the etiology and pathogenesis of RA that placed the T cell at the center of this disease. By the end of the 1980s a substantial body of evidence had accumulated that justified construction of a "T cell paradigm" for RA, and this model has formed the basis for trials of biologic therapies and other novel immunotherapies in the treatment of this disease.

Observations used to support the concept of a central role of T cells in RA are listed in Table 1. Some are undisputed facts, which any comprehensive explanation for the pathogenesis of the disease must take into account. These include the abundance of T lymphocytes in the joint, the distinctive profile of surface markers on synovial T cells compared with peripheral blood, and the increased frequency of specific class II major histocompatibility complex (MHC) alleles in RA. Other observations listed in Table 1, however, are more controversial. The important role of T cells in animal models of inflammatory arthritis is of significance only insofar as such models are accurate representations of RA, which remains unproven. Improvement in RA with T cell–directed therapeutic approaches would perhaps have been accepted as a well-demonstrated fact 10 years ago, but has been increasingly doubted due to more recent data. Whether the T cell repertoire in RA displays a reproducible pattern of oligoclonality and whether synovial T cell responses to identifiable antigens are important in RA remain points of confusion and controversy. On these issues the available data may as easily provide evidence against a role for T cells as they do in favor of such a role.

Table 2 summarizes key aspects of the current evidence against the importance of T cells in RA. It is of course difficult to prove that a specific autoantigen causes a human autoimmune disease, but in RA (unlike certain other human autoimmune conditions such as myasthenia gravis, autoimmune thyroid disease, and multiple sclerosis), strong evidence for the importance of any specific autoantigen is not yet available. In the absence of an autoantigen, attempts to identify oligoclonality and specificity in RA T cell populations have not yielded clear answers that illuminate disease pathogenesis. Moreover, the paucity of some T cell cytokines and the contrasting abundance of monokines has led to the view that RA (at least in its late stages and perhaps in all stages) is a disease in which the key cellular elements are monocytes and synoviocytes. In this view, T cell responses may be an interesting but essentially unimportant by-product of synovial inflammation and destruction.

In the present review, several aspects of the biology of the T cell in RA will be considered in the context of currently changing concepts about the pathogenesis of this disease. The focus will be primarily on studies of human disease rather than on animal models, and will emphasize recent observations. Consideration of these issues is not only of importance in understand-

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Table 1. Evidence for the importance of T cells in RA*

1. Abundance of T cells in synovial tissue and fluid.
2. Selective accumulation in the joint of specific T cell subsets defined by differentiation and activation markers.
3. Linkage of RA to specific class II MHC alleles.
4. Important role of T cells in animal models of inflammatory arthritis.
5. Improvement in RA with T cell–directed therapeutic approaches (?).
6. Presence of expanded oligoclonal T cell populations in RA (?).

* RA = rheumatoid arthritis; MHC = major histocompatibility complex.

ing RA, but should also bear upon appropriate directions for innovations in its therapy.

The synovial T cell population: clonal or heterogeneous?

The association of RA with a class II MHC epitope implies that antigen-specific responses of CD4+ T cells are required for the development of this disease. If such clones could be identified in human RA, as they have been in various animal models, rational targeted approaches to immunotherapy would be possible. Efforts have therefore been directed at analysis of the T cell population in the lesion, with the goal of detecting T cell receptors (TCR) that are preferentially used in RA and that might identify antigen-specific clones important in the pathogenesis of the disease. Experimental approaches used to tackle this question have included analysis of TCR gene rearrangements, detailed investigation of the repertoire of messenger RNA (mRNA) expression for the various T cell receptors, and direct immunologic analysis of receptor families expressed on the T cell surface. For the most part these studies have focused on the β chain rather than the α chain. Only a few of the dozens of studies in this area are cited in this review.

Results of this work have thus far been notable for their contradictory and confusing nature. Earlier work that used Southern blot analysis to detect oligoclonal populations led to disparate conclusions (2,3). Some of these discrepancies were reconciled by the subsequent finding that oligoclonality, when detected, is present only among synovial lymphocytes that respond to interleukin-2 (IL-2) and therefore must express high-affinity IL-2 receptors (4,5), a subset that includes only a small minority of synovial T cells (6).

Many of the more recent studies of the RA TCR repertoire have used polymerase chain reaction (PCR) amplification of complementary DNA corresponding to TCR β chain (and in some studies, α chain) mRNA expressed by the entire T cell population in RA synovial fluid, tissue, or peripheral blood (for recent review, see ref. 7). This approach has allowed quantitative analysis of the level of expression of each Vβ family. In some instances, sequencing has been performed on individual Vβ transcripts. Several of these studies have suggested increased or decreased usage of particular Vβ families, but the results have not been consistent among the different studies (8–15). Particularly striking results were obtained by Paliard et al, who found marked depletion of Vβ14-positive cells from peripheral blood, with readily detectable Vβ14 expression in the synovial compartment (16). Possible interpretations of such results include superantigen activation of this Vβ family in the periphery, with either migration of activated cells into lesional tissues or death of such cells. Some other investigations have also shown increased usage of Vβ14 or the related Vβ3 or Vβ17 TCR families in synovial fluid or tissue (9,10,12,14), although the results have often been more subtle than those observed by Paliard and colleagues (8,10,12), have been confined to Vβ3 and/or Vβ17 (14), or have been restricted to synovial fluid, not synovial tissue (12). Other studies have shown overrepresentation of different Vα or Vβ families, but not Vβ3, Vβ14, or Vβ17, in RA synovial fluid (11,13,15).

Thus far, analysis of the Vβ repertoire expressed in the synovial compartment has not helped to implicate specific antigens in the etiology or pathogenesis of RA. However, the frequency of antigen-specific cells in antigen-driven lesions can be $<1\%$ of the total T cell infiltrate. Therefore, current data do not exclude the possibility of a critical role for antigen-specific clonal T cell responses in the initiation or progression of RA.

An alternative approach to quantitating TCR V-region usage in RA, which avoids technical problems associated with PCR, is to determine the percent of T cells that express TCR subtypes by flow cytometry.

Table 2. Evidence against the importance of T cells in RA*

1. T cell responses to specific antigens have not been shown to trigger RA.
2. Demonstration of oligoclonal T cells in RA has been difficult, and different oligoclonal populations appear in different patients.
3. T cell–derived cytokines are less abundant in the joint than are cytokines produced by other cell types.
4. Erosion of cartilage and bone does not always correlate with inflammation, and may become independent of regulation by T cells.
5. Depletion of T cells by monoclonal antibodies may not be therapeutic in RA.

* RA = rheumatoid arthritis.

Results of such studies have not been consistent thus far, with Vα2 (17) or Vβ17 (18) preferentially used by synovial fluid T cells, and skewed representations of various Vβ receptor families among CD4+ or CD8+ T cells in synovial tissue (19).

A more detailed and laborious approach to understanding the RA T cell population involves sequencing receptor gene segments utilized by individual T cells. The third complementarity-determining region (CDR3) of the TCR β chain, which includes the V–D–J junctions, interacts directly with peptide bound in the MHC groove, and has been the principal target of such analyses (for review, see ref. 7). Taken together, the results suggest that the T cell response in RA synovial fluid or tissue, although heterogeneous, is focused in a manner distinct from that in normal peripheral blood or RA peripheral blood, and is characterized by a tendency for certain amino acids, such as valine, to be used more frequently in the CDR3 (7,20,21).

Although it has been proposed that skewed TCR usage in RA is confined to the joint, more recent studies suggest that the peripheral TCR repertoire may also be abnormal (22,23), in both the CD4+ (22,23) and CD8+ (24) subsets. However, a study of monozygotic twins discordant for RA revealed no differences in the peripheral Vβ repertoire (25). If the TCR repertoire is indeed abnormal in RA, this could be due to effects of MHC alleles during T cell development (see below), selective outgrowth of a subset of T cell clones stimulated by as-yet-unidentified antigen(s) and/or superantigen(s), or immunologic perturbations that are a consequence of local and systemic inflammation. The possibility that unusual manipulations of the immune system produce TCR repertoire skewing is illustrated by the appearance of new oligoclonal T cell populations in both RA blood and synovium following monoclonal antibody depletion of T cells in vivo (26). Expansion of certain T cell subpopulations when RA synovial T cells are injected into joints of SCID mice could reflect a similar mechanism (27).

Clonally expanded subsets of lymphocytes, present among RA B cells (28–30) as well as RA T cells, are not necessarily specific for self or foreign antigens important in disease pathogenesis. Instead, they may be markers for immunoregulatory disturbances that are nonspecific and that foster random outgrowth of various lymphocyte clones. A recent report suggests that defective regulation of clonal T cell proliferation or survival is common in RA but not in psoriatic arthritis, is readily detectable in peripheral blood lymphocytes studied using sensitive techniques, is present in unaffected family members of RA patients, and could be an inherited trait that is a risk factor for RA (31).

It is also possible that intercurrent infections, subclinical or overt, may affect the lymphocyte repertoire expressed in an autoimmune lesion, to a noticeable degree. Thus, T cells bearing TCR β chains that include a specific Vβ segment, activated by microbial superantigens or nominal antigens at sites distant from the joint, may, during the course of activation, express augmented levels of various adhesion molecules. Such cells would then migrate through activated endothelium in inflamed synovium and accumulate in the joint. Nonspecific and cytokine-mediated activation mechanisms may be sufficient to cause such populations to persist for weeks or months in autoimmune lesions. Thus, the finding of common Vβ expansions in patients followed up at one center during one period of time may be an "imprint" of pathogens epidemic in that community in the previous weeks or months. Other patient groups studied in geographically distant areas or at different points in time would be expected to show different "imprints." Such phenomena could be linked to periodic flares of disease, but may offer no clue to etiology and early pathogenesis. In this view, the RA synovium, as a result of chronic inflammation, becomes a lymphoid organ that reflects systemic immune responses. Appropriate control lymphocyte populations for lymphocyte repertoire analysis might be found in lymph node or spleen, not peripheral blood.

MHC alleles in RA: implications for the role of T cells

The MHC gene cluster is understood in considerable detail, and the terminology used to describe its individual polymorphic genes and their protein products has changed in recent years. A recent review describes the current nomenclature for MHC alleles (32). Although specific MHC polymorphisms are risk factors for the development of a variety of human diseases, including RA, the mechanism(s) for such associations remains uncertain. Since the primary known function of class II MHC is to present antigen to CD4+ T cells, it seems likely that the association of RA with a specific class II MHC sequence, termed "the shared epitope" (33), provides a clue to a role for T cells in the pathogenesis of RA. Recent work has even suggested that alternative amino acid residues at position 71 of DRB1 correlate with clinical subsets of RA (34). Moreover, binding studies have identified distinctions between peptides that can be externally inserted into RA-associated cell surface DR molecules compared with non–RA-

associated DR (35). Such distinctions include a limited number of peptides derived from the sequences of potential autoantigens such as type II collagen and the 65-kd heat-shock protein (36).

It would be premature, however, to deduce that the RA-associated DRB1 epitope triggers disease by presenting an arthritogenic peptide to T cells. The repertoire of peptides displayed by each MHC allele can be investigated by isolating and sequencing the peptides directly, using homozygous cell lines. Unique peptides that are displayed selectively by RA-associated DRB1 molecules have not been found with this approach, although peptides that are displayed only by non–RA-associated DRB1 molecules have been identified (37). Recent studies also suggest that the presence of 2 copies of RA-associated DRB1 epitopes confers greater risk of disease and augmented disease severity compared with 1 epitope (38–41). Such findings provide evidence, although not conclusive, against presentation of an arthritogenic antigen by DR, since this should operate in a strictly dominant manner. Alternatively, the "shared epitope" could augment risk for RA by *failing* to present an antigen that the immune system must recognize in order to prevent RA. In this view, non–RA-associated DRB1 alleles would be protective, and activation of T cells would be triggered by antigen(s) presented by non-DR MHC molecules, such as DP, DQ, and class I. A similar hypothesis has been formulated based on the findings that HLA–DQ8 confers susceptibility to collagen-induced arthritis in a transgenic mouse system and that alleles of the polymorphic H-2E locus (the murine homolog of HLA–DR) confer protection from disease (42).

Other mechanisms proposed to explain the linkage of RA with the MHC have focused on the QKRAA amino acid sequence (or similar sequences) at positions 70–74 of HLA–DRB1 alleles that are RA associated. Certain microbial antigens, including a bacterial heat-shock protein, also contain the QKRAA sequence, and are recognized by synovial fluid T cells from patients with early RA (42). Since peptides derived from MHC molecules can themselves be presented as antigens to T cells, it has been suggested that DRB1 peptides containing QKRAA can function as antigens that participate in positive selection of T lymphocytes in the thymus. Such cells would subsequently respond to microbial antigens with shared peptide sequences, and cross-react with putative autoantigens in the joint (43).

Direct analysis of the TCR repertoire expressed by naive, CD4+ peripheral blood T cells has indeed indicated differences between individuals who possess HLA–DRB1* 04 (an RA-associated allele) and control subjects who are B1*04 negative (44). Further differences were found between B1*04-positive individuals with RA versus those without RA (44). Although these results were interpreted as being due to events occurring during thymic selection (44), alternative explanations are possible since the expressed TCR repertoire could be altered by post-thymic selection mechanisms. No link has yet been made between the specific capabilities of the RA TCR repertoire and responses to putative autoantigens that might be important in RA. Although one recent report suggests that an allelic polymorphism in the TCR β locus is linked to an independent genetic risk factor for RA that acts in synergy with HLA–DR4 (45), the exact nature of this locus has not yet been specified.

Table 3. MHC and RA: possible mechanisms for a link*

1. Specific binding of self-antigen.
2. Creation of holes in the repertoire by inability to present specific antigen to T cells.
3. Cross-reactivity between foreign antigen and MHC.
4. Regulation of positive and negative selection of T cells.
5. Altered mechanisms of MHC intracellular trafficking and peptide loading.

* MHC = major histocompatibility complex; RA = rheumatoid arthritis.

A novel explanation for the association of QKRAA-containing DR molecules with RA has recently been proposed (46). It was found that an endogenous 73-kd heat-shock protein bound selectively to such DR molecules through the QKRAA motif (46). Such intracellular binding could alter loading or presentation of antigens, or impede surface expression of the DR molecules. A hypothesis to link such a phenomenon to RA has not yet been proposed, but could involve failure to present a protective antigen, as outlined above. Resolving the mechanism(s) by which MHC alleles affect the risk of developing RA (Table 3) should yield insight into the role of T cells in RA and perhaps provide clues to the etiology of the disease.

Synovial T cells: subsets, surface markers, and activation pathways

Synovial fluid and synovial tissue T cells differ from normal or RA peripheral blood T cells in the expression of specific surface markers. Differential expression of CD45 isoforms has been one method of distinguishing "naive" from "memory" T cells, and CD45 isoforms characteristic of memory T cells are

expressed more extensively in the synovial compartment than in peripheral blood (47,48). The interpretation of CD45 isoform pattern expression is complex, because these isoforms are regulated both by differentiation of functional T cell subsets and by T cell activation.

The TCRγ/δ TCR T cell subset, generally a small minority of the total T cell population, comprises 4–6% of RA synovial fluid T cells (49,50) and perhaps a higher proportion of synovial tissue T cells (51). Although the role of γ/δ T cells in RA is not yet understood, the range of antigens to which such cells can respond may provide an intriguing clue to a unique role in autoimmunity (52–55). Thus, recent findings have established that γ/δ T cells can recognize novel nonpeptide antigens (55), as well as typical peptide antigens, heat-shock proteins, and superantigens (52–54). Mechanisms of antigen presentation, receptor costimulation, and intracellular signaling may all have unique properties in γ/δ T cells (54–56). Subsets or clones of γ/δ T cells may be expanded in the synovial fluid of some RA patients (57,58), but the in vivo mechanisms responsible for this are not yet established. Animal studies have indicated that, depending upon the stage of disease, γ/δ cells may serve either a regulatory or a pathogenic role in models of inflammatory arthritis (59,60). It is not yet known whether this is also the case in human RA.

A growing number of T cell membrane glycoproteins, such as CD28, have been implicated as having roles in costimulating or regulating T cell activation. Synovial T cells can functionally express not only CD28, but also CD28 ligands (61–63). However, in some RA patients, an expanded subset of CD4+, CD28− cells has been identified in the peripheral blood, and, to some extent, in the joint (64). These cells respond in the autologous mixed lymphocyte reaction (i.e., are autoreactive) (64), and their costimulatory receptors are not yet known.

Another structure that can convey co-activating signals is CD6 (65), which is expressed on most T cells and which may play an important role in T cell autoreactivity (66). One CD6 ligand, termed ALCAM, has been identified (67), and indirect evidence for other CD6 ligands has been obtained (68). ALCAM is expressed much more strongly by keratinocytes and synoviocytes than on peripheral blood antigen-presenting cells (APC) (ref. 68 and Singer NS, Fox DA: unpublished data).

A surface structure termed CD60, identified by a monoclonal antibody generated against an RA synovial T cell line (69), could also have a role in activation of synovial T cells. CD60 is expressed on a minority of peripheral blood T cells but on a majority of T cells in autoimmune lesions, in synovium or in skin (6,69,70), and on nonlymphoid cells with which T cells interact in thymus, skin, and synovium (6,70–72). Antibody to CD60 is mitogenic or comitogenic for T lymphocytes, including T cell clones derived from RA synovial fluid (69,70,72,73). Although the CD60 antigen appears to be a marker for T cells that accumulate in autoimmune lesions, the mechanism for this preferential expression is not clear, since CD60, unlike class II MHC, is not induced by activation of T cells (69,73). It is possible that CD60 contributes to homing of T cells to sites of inflammation, that cytokine-directed differentiation of T cells enhances CD60 expression (74), or that a ligand for CD60 is mitogenic for such T cells following their entry into synovium, therefore expanding this population selectively. T cell receptors for extracellular matrix molecules found in synovium may also play a role in costimulation of T cell proliferation (75). The importance of non-TCR activating pathways for T cells in RA is also emphasized by the suggestion that signal transduction through the TCR is defective in RA (76).

Origin and fate of synovial T cells

The extent to which activation of synovial T cells occurs prior to entry into synovium (in lymph nodes, gut-associated lymphoid tissue, spleen, circulation, or other systemic sites), during the process of transendothelial migration into inflamed synovial tissue, or following entry into the synovium is not yet known. Also unknown is the life span of a synovial T cell, and under what circumstances such cells undergo apoptosis. Apoptosis can be induced ex vivo in synovial fluid T cells through the CD95/Fas molecule, but has been difficult to detect in lymphocytes in synovial tissue sections (77). It seems likely that T cells can return from the synovium to the circulation, but this process is not yet well characterized. Within the joint, there appear to be subtle differences in subset distribution between perivascular lymphoid aggregates, other areas of the synovium, and synovial fluid. Presumably, cells move from the lymphoid aggregates out into the remaining areas of synovial tissue, and then into synovial fluid. However, this sequence of events has not been well studied, and it is not known whether reverse migration of cells can also occur.

The location of T cells may be relevant to their functional responses, since different types of APC are concentrated in different regions of the synovial tissue or in synovial fluid. Unique properties of APC subsets (monocytes, macrophages, B lymphocytes, dendritic

cells, fibroblasts, and other populations) likely include restricted expression of specific costimulatory molecules and distinct profiles of secreted cytokines, which together would play a defining role in the resulting T cell functional program. Potential interaction with a broad range of APC is facilitated by T cell differentiation to the memory phenotype (78), characteristic of most RA synovial T cells.

Critical to the influx of T cells and other inflammatory cells into the joint is up-regulation, expression, and function of an array of leukocyte endothelial cell–cell interaction molecules, collectively termed adhesion molecules. The role of such structures in RA has recently been reviewed in detail (79). Molecules relevant to the migration and retention of T cells in synovium probably include integrins and their ligands, selectins and their ligands, CD44, and other structures. Although indirect evidence suggests that unique receptor–ligand interactions may direct lymphocytes into synovial tissue (80), molecular identification of such synovium-specific structures has not yet been accomplished. However, quantitative differences in the relative expression of E-selectin and intercellular adhesion molecule type 1 (ICAM-1) by RA synovial endothelium versus other vascular endothelial populations has been described (81). Animal model systems have proven useful for describing the sequence of up-regulation of adhesion receptors on lymphocytes and other leukocytes that migrate into synovium (82) and for demonstrating the feasibility of therapeutic interruption of migration of such cells into synovium using monoclonal antibodies or soluble ligands (83–85).

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, monocytes derived from peripheral blood, and B lymphocytes. Comprehensive reviews of synovial dendritic cell (86) and fibroblast (87) function have recently appeared in *Arthritis & Rheumatism*. Recent data suggest that all of these cell types might serve as APC or accessory cells for T cell activation, including not only the "professional APC" that are bone marrow derived, but also the synovial fibroblasts (88–90). Experiments using T cell mitogens that do not require MHC identity between APC and T lymphocytes (superantigens or lectins) suggest that type B synoviocytes possess accessory cell function of a potency comparable with that of professional APC (89).

The ranges of ligands for costimulatory T cell surface structures that are expressed by various synovial APC are distinct. For example, type B synoviocytes lack ligands for CD28, but do express ligands for CD2 and lymphocyte function–associated antigen 1 (LFA-1) that are important in superantigen-induced T cell activation (89). The LFA-1 molecule (CD11a/CD18) on synovial fluid T cells is in a high avidity state, apparently induced by a factor present in synovial fluid (91), and it seems likely that synovial tissue T cells would also express an activated form of LFA-1. Superantigens can also trigger production of inflammatory mediators by synoviocytes, following up-regulation of the inducible isoform of cyclooxygenase, cyclooxygenase-2 (92).

Type B synoviocytes and T cells can also interact in the absence of superantigen (89,93,94). A factor secreted by synoviocytes, not yet identified, promotes survival of activated T cells (93). Unactivated lymphocytes can adhere to interferon-γ (IFNγ)–treated synoviocytes (89,94), although less strikingly than in the presence of superantigen (89). Such adhesion is mediated by vascular cell adhesion molecule type 1 (CD106) and ICAM-1 (CD54), which are strongly expressed by synoviocytes (89,94). Glucocorticoids inhibit both expression of these molecules and cell adhesion (94), suggesting one plausible mechanism for the therapeutic effects of intraarticular steroids, and possibly also systemic steroids, in RA.

Production and utilization of cytokines by RA synovial T cells

Cytokines play a dominant role in the pathophysiology of joint inflammation and destruction in RA (95,96), and the results of recent studies suggest that interfering with the function of cytokines, particularly tumor necrosis factor, may be an effective approach to therapy both in rodent models and in human RA (97,98). Monocyte-derived cytokines contribute to activation of T cells, other leukocytes, and endothelium, and to joint damage and remodeling, the latter through effects on synoviocytes and chondrocytes (99).

The cytokine repertoire of synovial fluid and synovial tissue T cells is not well understood, and lack of high levels of IL-2 production in the synovial compartment has raised doubts about the role of T cells in RA (100). Whether Th1 or Th2 cells predominate is controversial (101,102). In one study (103), synovial γ/δ cells were found to have different cytokine production profiles than α/β cells (less IFNγ and IL-10, but more IL-4). The Th1/Th2 model of distinct T cell cytokine profiles

may prove difficult to apply to diseases such as RA, since individual T cells can adapt more than one cytokine profile and production of individual cytokines can be independently regulated (104).

Recent information about 3 cytokines found in RA synovium, IL-10, IL-15, and fibroblast growth factor 1 (FGF-1), may help explain apparent paradoxes about the biology of RA synovial T cells. IL-15 is a cytokine with a secondary structure (but not primary sequence) similar to that of IL-2. Like IL-2, it has T cell activating properties, and it uses a receptor complex that shares 2 of its 3 subunits with the IL-2 receptor (105). Unlike IL-2, it is not produced by T cells, but instead from a variety of sources including fibroblasts and monocytes (106). Most significantly, it is abundant in the joint (unlike IL-2), and has a range of mitogenic and chemotactic activities that are likely important in influx and activation of T cells in synovium (106).

A recent report also suggests that FGF-1 may be important in activation of RA synovial T cells (107). FGF-1 is abundant in the joint, and FGF-1 receptor–bearing T cells are common among CD4+ cells in perivascular infiltrates in RA synovium. Moreover, a higher proportion of peripheral blood T cells from RA patients was activated by FGF-1, compared with cells from normal subjects or patients with systemic lupus erythematosus.

It is now believed that a major reason for the relative paucity of IL-2 in the RA joint is the production in synovium of IL-10, which suppresses synthesis of Th1 cytokines. Elevated levels of IL-10 are found in RA synovial tissue, synovial fluid, and serum (108–110). IL-10 is likely produced by non–T cells in synovium and peripheral blood (108–110), and possibly also by synovial T cells, which, at a clonal level in vitro, can produce high levels of both IL-10 and IFNγ (111). Evidence for antiinflammatory effects of IL-10 both in collagen-induced arthritis in mice (112) as well as in cell culture systems using RA synovial fluid mononuclear cells (113) has prompted consideration of the use of IL-10 as a novel therapeutic agent in RA. This would be based on the premise that the high levels of IL-10 in RA synovium are not quite sufficient to achieve its antiinflammatory effect. Our understanding of the biology of IL-10 is probably not yet sufficiently complete to predict its therapeutic potential in chronic RA.

New directions in the treatment of RA: should T cells be the targets?

Efforts to treat RA by depleting T cells using monoclonal antibodies or immunotoxins have generally been disappointing (114–119). Particularly problematic has been the lack of correlation between the biologic effects of such "high-tech" therapies (elimination of lymphocytes) and clinical responses. One potential explanation is insufficient depletion of synovial T cells to a level below the minimum threshold needed to sustain joint inflammation (120,121). In this regard, it is of interest that profound CD4 T cell lymphopenia, in the setting of the acquired immunodeficiency syndrome, does not necessarily suppress RA (122), contrary to previous impressions. Enumeration of CD4+ cells in synovia of such patients would be informative.

Other T cell–directed approaches might target antigen-specific responses. Such strategies are based on the effectiveness of induction of tolerance to tissue-specific antigens, such as type II collagen, in animal model systems (123), or induction of immunoregulatory circuits using vaccination with specific TCR peptides (124). Transferring such strategies to genetically diverse humans with established disease involves many hurdles. A preliminary study of oral type II collagen in the treatment of RA appeared to show significant benefit in a subset of patients with established disease (125), but a subsequent larger study in patients with early RA showed only minimal benefit that was not statistically significant (126). Results of an ongoing multicenter trial should be available soon. Another novel approach involves infusion of allogeneic leukocytes, in an attempt to duplicate pregnancy-induced immunosuppression of RA (127). At this time, understanding of the biologic and clinical effects of this strategy is rudimentary, and much more information will be needed to evaluate its possible role in treating RA.

If specific infectious agents can ultimately be identified as the cause of RA, therapy directed at the specific organisms and/or the immune responses to such organisms should be useful. Infection with human T lymphotropic virus type I (HTLV-I) has been shown to be associated with an RA-like syndrome in Japan (128,129). HTLV-I can infect synoviocytes as well as T cells (130), and can induce joint inflammation in rodents (131). However, in most RA patients, there is no convincing evidence linking the disease to retroviruses, mycoplasmas, or other pathogens.

Conclusion

The T cell–centered paradigm for RA, as it was formulated approximately 10 years ago, now seems outdated. In light of unimpressive levels of T cell cytokines in synovium and unimpressive clinical results

of therapeutic T cell depletion, reasonable arguments that depict the T cell as relatively unimportant in RA, especially in chronic disease, have been advanced. Concurrently, intensive analysis has failed to identify pathogenic antigen-driven T cell clones in the joint in human RA. However, increased understanding of two broad classes of molecules should now prompt development of a new model for the role of T cells in RA.

The first class of molecules is the growing list of membrane structures that transmit costimulatory signals to the T cell, based on direct interaction with cell surface ligands on other cells—not only on dendritic cells, monocytes, and B cells, but also on parenchymal cells such as fibroblastic synoviocytes. The notion that synovial T cell responses in RA are driven by autoantigens presented to the immune system by the shared epitope needs to be reevaluated. Some recent data are more consistent with the notion of an indirect role for the shared epitope in RA and with a polyclonal T cell response in the joint triggered by antigens displayed by non-DR MHC molecules in conjunction with activation signals delivered by costimulatory ligands.

The second class of molecules is the cytokines—the local and systemic hormones of immunity, inflammation, and host defenses. The number of known cytokines and their receptors has grown remarkably in the last decade. Recent information about the abundance and function of some of the newer cytokines in RA synovium, especially IL-10 and IL-15, may resolve apparent paradoxes about the role of T cells in RA and allow construction of a better-informed, more convincing T cell paradigm. This paradigm should involve a sequence of pathologic cell–cell interactions in RA, which result in conversion of the synovium from an organ focused on maintaining local tissue homeostasis to an organ that becomes a component of the systemic lymphoid system, and eventually to a partially transformed, invasive, and destructive chronic inflammatory tissue. Future novel therapeutic approaches to RA that are specific, safe, and effective will disrupt one or more of the pathologic cell–cell interactions essential for this sequence of events, rather than directly eliminating one of the participating cell populations.

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