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POTENTIAL ROLE OF γδ T CELLS IN AUTOIMMUNE DISEASES

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More than half a decade after their identification, γδ T cells continue to challenge immunologists. Their antigenic specificity, antigen recognition process and biological role are still largely elusive. Paradoxically, increased frequencies of γδ T cells can be found in two apparently polar situations: immunodeficiency on the one hand, and hyperimmune states such as autoimmunity and inflammatory conditions on the other hand. The hypothesis presented here postulates that γδ T cells, vital remnants of a primitive cellular immune system, are called upon in situations where the more evolutionarily advanced and "sophisticated" cellular immune barrier, the αβ T-cell-dependent system, is failing. Under certain circumstances, this may result in autoimmunity.

It has long been noticed that immunodeficiency and autoimmunity, two apparently conflicting clinical situations, can co-exist. For example, patients with agammaglobulinaemia have a higher frequency of arthritis clinically indistinguishable from rheumatoid arthritis (RA) (Good *et al.*, 1957). Patients with selective IgA deficiency have a greater than expected occurrence of systemic lupus erythematosus (Cassidy *et al.*, 1969) and insulin-dependent dia-

betes mellitus (Hoddincot *et al.*, 1982). Autoimmune phenomena have also been observed in patients with AIDS (Kopelman and Zolla-Pazner, 1988; Berman *et al.*, 1988). In addition, rodents rendered immunodeficient by cyclosporine A, by total lymphoid irradiation or by anti-T-cell antibodies may develop autoimmune sequelae (Trentham *et al.*, 1984; Sakuguchi and Sakaguchi, 1988, 1989).

T cells bearing the γδ T-cell receptor (TCR) have been identified in higher frequencies in spontaneous or induced immunodeficiencies. Patients with ataxia teleangiectasia, a syndrome associated with immunodeficiency, have been reported to display a high frequency of γδ T cells in their peripheral blood (Carbonari *et al.*, 1990). In addition, some patients with Wiskott-Aldrich syndrome and severe combined immunodeficiency have up to 68 % circulating γδ T cells (Morio *et al.*, 1990). Long-term γδ T-cell lines were isolated from a patient with immunodeficiency (Brenner *et al.*, 1987). Immunodeficiency induced by cyclosporine A in mice is associated with a relative increase in γδ cells (Jenkins *et al.*, 1988). Taken together, the above observations may suggest that inherent or acquired defects in development or function of TCR αβ cells may create suitable conditions for less "sophisticated", potentially autoaggressive cells, such as TCR γδ cells, to expand and result in autoimmunity.

Could "spontaneously" occurring autoimmune conditions which have no clinically apparent immunodeficiency, such as RA, stem from a similar pathogenetic mechanism? TCR γδ cells and cells with the phenotype $CD3^+ CD4^- CD8^-$ ("double-negative" cells, which are mostly TCR γδ cells) have been implicated in a number of hyperimmune conditions in mice including models of lupus (Datta *et al.*, 1987) and autoreactivity (Morriset *et al.*, 1988). Double-negative murine T cells were found capable of breaking oral tolerance (Kitamura *et al.*, 1987). In humans, double-negative cells have been found in thyroid tissue in Hashimoto thyroiditis (Del Prete *et al.*, 1986). Abundance of double-negative TCR γδ cells has also been noticed in the lungs of patients with sarcoidosis (Balbi *et al.*, 1990) and in the synovial fluid of patients with RA (De Maria *et al.*, 1987; Brennan *et al.*, 1988a; Haynes *et al.*, 1988; Holoshitz *et al.*, 1989; Reme *et al.*, 1990).

The role of γδ T cells in the pathogenesis of RA has not been defined yet. However, a number of observations suggest that they may be pathogenically important. T cells in general are thought to play an important role in the pathogenesis of RA. Histologically, the synovial membrane in RA is infiltrated by T lymphocytes, predominantly of the $CD4^+$ phenotype. These T cells show markers of activation such as receptors for IL-2 and HLA class II molecules (Klareskog *et al.*, 1982). Selective elimination of $CD4^+$ T cells by procedures such as total lymphoid irradiation (Tanay *et al.*, 1987) can lead to improvement of the disease. The specificity of synovial T cells is unknown. While an antigen-non-specific T-cell activation may play a role in perpetuation of the disease (Haynes *et al.*, 1988), the close association of RA with certain HLA DR alleles suggests that recognition of an arthritogenic antigen may be involved in triggering the disease.

Two-thirds of patients with seropositive RA display the HLA DR4 phenotype (Stastny, 1978). Consistent with the "shared epitope" theory (Gregersen *et al.*, 1987), recent molecular data suggest that many of the remaining one-third of DR4-negative patients may share with the DR4-positives a typical nucleotide sequence at the third hypervariable region of the DRβ1 gene (Nepom *et al.*, 1989). This region of the class II β chain is predicted to comprise part of the class II helix critical for specific interaction with antigenic peptides and the TCR (Brown *et al.*, 1988). Mutations in this region have been shown to alter T-cell immune responses and susceptibility to autoimmune disease in mice (Christadoss *et al.*, 1985). Thus, it is conceivable that susceptibility to RA is related to the ability of these regions to present antigens to T cells.

As mentioned above, the identity of the putative antigen is still unknown. However, the possibility that mycobacterial heat shock proteins (HSP) are playing a role is emerging. Synovial T lymphocytes from patients with RA make a vigorous proliferative response to mycobacterial antigen, in particular to the 65-Kda mycobacterial HSP (Holoshitz *et al.*, 1986; Res *et al.*, 1988). These studies have shown that the proliferative responses to the mycobacterial protein were higher in synovial fluids than those in paired peripheral blood. The reactivity was characteristically found in early stages of joint inflammation, suggesting that T-cell reactivity to HSP may be involved in triggering the arthritis. Additional evidence for the potential arthritogenicity of HSP comes from studies of adjuvant arthritis, a rat model of RA. From rats afflicted with this disease, a T-cell line (Holoshitz *et al.*, 1983) and clones (Holoshitz *et al.*, 1984, 1988) capable of either transferring or protecting against arthritis have been isolated. These clones recognize an epitope within amino acids 180-188 of the mycobacterial 65-kDa HSP (Van Eden, W. *et al.*, 1988).

HSP are a family of highly conserved proteins which can be induced in prokaryotic and eukaryotic cells by heat or other stress conditions. While their biological role is not entirely understood, these findings have fostered the idea that antigenic mimicry might be involved in the pathogenesis of RA and other inflammatory arthritic conditions. According to this hypothesis, genetically susceptible individuals may develop an immune response to bacterial HSP that is cross-reactive with self. The resultant immune injury to target cells may in turn induce further expression of HSP and lead to chronic self perpetuation of the disease. However, it is possible that the reactivity of synovial T cells to mycobacterial proteins is an effect of the disease rather than a cause. It is possible that tissue injury in a variety of inflammatory arthritic conditions, regardless of the precipitating initial events, results in expression of new antigens on the synovial cell surface which cross-react with the mycobacterial antigens.

Given the close association between certain DR alleles and RA susceptibility, it would seem reasonable to predict that recognition of a specific antigen in the joint by αβ T cells would involve a clonally restricted population of T cells. An increasing body of evidence suggests that this is probably not the case. Initial studies using Southern blot analysis of TCR β genes showed distinct rearrangements in long-term cultured synovial T cells, suggesting clonal dominance (Stamenkovic *et al.*, 1988). However, the possibility that the long term tissue culture conditions in that study could have induced *in vitro* selection was suggested by the finding of similar clonal dominance in cultures obtained from patients with osteoarthritis (Stamenkovic *et al.*, 1988). Moreover, recent studies failed to demonstrate β-chain gene rearrangement in any one of 15 fresh synovial fluid cell preparations from RA patients (Keystone *et al.*, 1988) or predominant rearrangements among 40 RA synovial fluid T-cell clones (Duby *et al.*, 1989). Other recent studies reached similar conclusions (Savill *et al.*, 1987; Brennan *et al.*, 1988b). Although these results question the clonality of αβ T cells in RA synovial effusions, they do not exclude the role of antigen-specific T-cell responses in RA. It is possible that different TCR are capable of recognizing one or more epitopes on the target antigen. It is also possible that a small minority of antigen-specific T-cell clones initiate an autoaggressive process which can be perpetuated by recruitment and activation of a polyclonal T-cell population. These results provide a rationale for directing more attention to γδ T cells.

As mentioned above, synovial effusions of RA patients contain a high number of T cells bearing the γδ TCR. Their percentage in synovial effusions was found to be between two-fold to four-fold that in normal peripheral blood. Furthermore, in some of these studies (Brennan *et al.*, 1988a; Holoshitz *et al.*, 1989; Reme *et al.*, 1990), most, if not all, of the γδ T cells stained positively with the monoclonal antibody Ti -γA, which detects TCR γ chains with the particular rearrangement: Vγ9JγPCγ1 (Triebel *et al.*, 1988).

Thus, while there is no evidence for αβ clonality, a γδ T-cell population, possibly oligoclonal, preferentially accumulates in RA synovial fluids. It is quite interesting that peripheral TCR γδ T cells and TCR γδ cells isolated from synovial fluid and thymus were found to recognize mycobacterial antigens, including the mycobacterial 65-kDa HSP (Holoshitz *et al.*, 1989; Janis *et al.*, 1989; O'Brien *et al.*, 1989; Haregewoin *et al.*, 1989; Modlin *et al.*, 1989; Kabelitz *et al.*, 1990). With one exception (Haregewoin *et al.*, 1989), all studies have shown that reactivity of γδ T cells to mycobacteria was MHC-unrestricted. Studies of the structure of the TCR chains of mycobacteria-reactive T-cell clones revealed a limited receptor repertoire. For example, human mycobacteria-reactive γδ T-cell clones were found to uniformly express the Vγ9JγPCγ1 rearrangement, paired with Vδ2-bearing TCR δ chain (Holoshitz *et al.*, 1989; Kabelitz *et al.*, 1990; Holoshitz *et al.*, unpublished results), and murine mycobacteria-reactive γδ T cells all expressed the Vγ1JCγ4 rearrangement paired with a Vδ6-bearing δ chain (Happ *et al.*, 1989). Limited V-region usage and MHC non-restricted recognition of mycobacteria are reminiscent of bacterial "superantigen" recognition by αβ cells. Recent results from the author's laboratory indicate that, in addition to their reactivity to the mycobacterial superantigen-like moeity, γδ T cells can recognize nominal antigenic peptides (Holoshitz *et al.*, in preparation).

The basic hypothesis presented here is that TCR γδ cells and perhaps other "immature" cells play a role in triggering the synovitis of RA. It is hypothesized that RA-susceptible individuals cannot raise an adequate T-cell response to certain foreign antigens due to holes in their αβ T-cell repertoire. Patients with RA have been found to display an impaired immune response to EBV (Depper and Zvaifler, 1981) and tetanus toxoid (Devey *et al.*, 1987). In the case of EBV, sequence homology between the EBV glycoprotein gp110 and the third hypervariable region of the RA-associated DRβ1 chain was noticed (Roudier *et al.*, 1988). It is hypothesized that a number of potential RA-inciting antigens might have sequence homology with either the "bare" DRβ1 chain or with a combination of DRβ1 and a self peptide occupying the MHC groove. Due to self tolerance, these antigens would not be recognized by αβ T cells. Instead, they will be presented to γδ T cells by a relatively non-polymorphic RA-associated MHC molecule such as DRw53 (Merryman *et al.*, 1989) or by another non-MHC molecule in linkage disequilibrium with DR4. (Experimental data supporting such nominal antigen recognition are currently being accumulated in the author's laboratory.)

The vast majority of individuals with DR alleles that confer susceptibility to RA do not develop arthritis. In a small minority of individuals, this otherwise safe and effective γδ T-cell immune response may result in RA due to other, non-MHC genes (Go *et al.*, 1987). Such putative polymorphic genes may encode products capable of enhancing activation of γδ T cells and/or migration of these cells to the target organs. The accumulation of γδ T cells in the synovium may be due to *in situ* activation by either the nominal antigen, the mycobacterial superantigen, or self constituents of the joint mimicking those antigens. The locally activated γδ T cells could release lymphokines capable of polyclonal activation of αβ T cells (Ferrick *et al.*, 1989) and stimulation of macrophages (Modlin *et al.*, 1989), leading to the formation of a pannus. While γδ T cells would have a role in triggering the inflammatory process, according to this hypothesis, the effector role is played by polyclonal $CD4^+$ T cells. Elimination of such cells has been reported to yield temporary relief of RA (Tanay *et al.*, 1987).

In summary, it is hypothesized that γδ T cells are used as an alternative defence mechanism in situations of αβ T-cell-dependent immunodeficiency. An analogous situation of "limited immunodeficiency" may exist in RA when, due to their amino acid sequence homology to the DRβ chain, some foreign antigens are tolerated by αβ T cells. The impaired immune defence

against the foreign antigen is partially compensated by activated γδ T cells. The γδ T-cell response, augmented with the aid of non-MHC gene products, may result in arthritis. This hypothesis is not free of pitfalls; however, it offers a plausible explanation to some puzzling questions regarding RA and possibly other autoimmune conditions. It is conceivable that similar constellations of certain MHC alleles, foreign antigens and conducive non-MHC genes can be implicated in other MHC-associated autoimmune diseases.

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