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EDITORIAL REVIEW

Is there restricted T cell receptor usage in autoimmune disease?

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Tolerance to self-antigens is thought to be acquired during ontogeny and accomplished by a combination of clonal deletion and anergy of self reactive T cells. Autoimmunity develops following a breakdown in the mechanisms maintaining self-tolerance when autoreactive T cells that are present in all individuals become activated. Since T cells recognize antigen in the context of class I or class II MHC molecules, several therapeutic approaches are theoretically possible to try to ameliorate or prevent autoimmune pathology. If the autoantigen is known, there is the possibility of designing peptides that would prevent T cell interaction with the autoantigen or tolerize the autoreactive T cell. If the critical restriction element is known, antibodies to these MHC molecules may be used to block the immune response to the antigen. Finally, if there is evidence of restricted T cell receptor (TCR) usage, antibodies may be employed to eliminate these T cells specifically, or vaccination protocols may be developed to specific T cells bearing these receptors.

The possibility of specifically inhibiting T cells involved in autoimmune pathology while sparing those responding to wholly exogenous antigens is an attractive therapeutic option. Some experiments have implied that there might be some restriction of TCR usage by T cells involved in autoimmune pathology. These studies showed that it was possible to 'vaccinate' animals against the experimental induction of autoimmune disease using glutaraldehyde-fixed autoreactive T cell clones (Ben-Nun, Wekerle & Cohen, 1981). Concrete evidence for restricted Vβ usage by autoreactive T cells came from studies of experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis, which convincingly demonstrated that the T cell initiating this disease utilized Vβ8.2 in their TCR (Acha-Orbea *et al.*, 1988; Acha-Orbea, Steinman & McDevitt, 1989). Following on from these observations in mice a similar situation was shown to exist for rat EAE (Heber Katz & Acha-Orbea, 1989); and EAE in rats was shown to be prevented not just by vaccination with inactivated T cell clones but also by immunization with synthetic peptides of sequences found in CDR2 and CDR3 TCR γ regions (Vandenbark, Hashim & Iffner, 1989).

Additional evidence for restricted TCR usage emerged from studies of collagen-induced arthritis in mice and the spontaneous insulin-dependent diabetes of NOD mice. Genetic studies suggested that Vβ6 bearing T cells may be necessary for the induction of arthritis in mice (Haqqi *et al.*, 1988; Banerjee *et al.*, 1989). However, the interpretation of the data has been contested and at least one other group of investigators can find no evidence for a critical role for Vβ6-bearing T cells in this disease. The finding that T cell clones which could transfer diabetes in NOD mice used predominantly Vβ5 was interpreted as indicating a restricted usage of this β chain by T cells mediating destruction of pancreatic beta cells (Reich *et al.*, 1989). There has been some controversy concerning the validity of this observation, and several groups of investigators have failed to protect mice from disease by treatment with anti-Vβ5 antibodies.

In light of the animal studies on EAE, it seemed appropriate to search for evidence of such restricted TCR usage in human autoimmune conditions. Studies have been carried out to determine whether there is any evidence of biased usage of particular Vβ chains by T cells isolated from peripheral blood of patients with a variety of autoimmune conditions or from the synovial fluid or membrane of the rheumatoid joint. Two papers presented in this issue of *Clinical and Experimental Immunology* (Koitiainen *et al.*, 1991; van Laar *et al.*, 1991) exemplify the approaches that have been used and the controversy which exists. Using antibodies against three Vβ families, Kontiainen *et al.* (1991) provide evidence of oligoclonal proliferation of activated T cells in the peripheral blood of patients in insulin-dependent diabetes mellitus (IDDM). In individual patients, however, different Vβ families were expanded. In contrast no such oligoclonality was consistently observed in the peripheral blood T cells or in the T cells isolated from the synovial tissue of fluid of patients with rheumatoid arthritis. T cells were examined for the presence of dominant TCR rearrangements in the studies of van Laar *et al.* (1991) and a dominant rearrangement was only seen in two out of 16 synovial T cell isolates. This is consistent with the studies of some investigators (Savill *et al.*, 1987; Keystone *et al.*, 1988; Duby *et al.*, 1989) but differs from the work of Stamenkovic *et al.* (1988) and Mittenburg *et al.* (1990). Van Laar *et al.* (1991) additionally make the point that the different methods employed for isolating T cells from the synovial membrane (enzyme digestion *versus* outgrowth of cells) may influence the result.

Other studies have addressed Vα chain usage by T cells in autoimmune pathology. Post-mortem brain tissue from patients with multiple sclerosis (MS) has been examined for the presence of T cells with restricted use of T cell receptor gene products (Oksenberg *et al.*, 1990). TCR gene usage in areas of demyelination was assessed following amplification of cDNA by polymerase chain reaction using TCR primers specific for T cell receptor Vα and Cα sequences. TCR transcripts were detected by this method in the brains of MS patients; they were not found in control brain material. Examination of three different MS

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patients revealed usage of a restricted number of Vα families as well as the presence of Vα10 transcripts in every patient. Furthermore, sequence analysis of transcripts showed that the Vα12.1 region was rearranged to a limited number of Jα region segments, supporting the contention that TCR Vα gene expression within lesions in the brains of MS patients might be restricted. This conclusion is based on a study involving a limited number of patients, and the overall conclusions may change when more pathological material is examined.

Since many of the T cells at the site of inflammation have arisen by secondary recruitment and may not be involved in pathology it is important to be able to establish a pathological role for the T cells under investigation. In the murine systems it is possible to establish whether the T cells under observation are indeed pathologically relevant by demonstrating that they can transfer disease passively. It is also possible to substantiate a claim for restricted Vβ usage by demonstrating disease prevention by anti-Vβ antibody. This is clearly problematic in humans. Furthermore, in humans it is often impossible to gain access of the site of the pathological lesion and therefore studies are often carried out on peripheral blood samples. Analyses of the peripheral T cell repertoire may not reveal the correct picture. This is exemplified from the results obtained in the EAE model in which it has been found that despite clear proof of the involvement of Vβ8-bearing T cells in the primary autoimmune response there is no increase in T cells expressing this receptor in the periphery. Furthermore, the majority of Vβ8-bearing T cells in the lymph node of immunized mice are specific for PPD (David Wrath, personal communication).

It is often difficult to extrapolate from the findings obtained in animal models to human conditions. Many of the studies on TCR usage in animals detect an involvement of a restricted T cell repertoire in the initiation or early stages of autoimmune disease. There is no information regarding the use of Vβ8-bearing T cells during the relapsing phase of EAE in murine models, and it is not impossible that following some initial stress or trauma responses to other autoantigens occur and the response becomes more heterogeneous. In humans all the analyses will be performed after the autoimmune response is underway, and in many cases after several episodes of disease. A substantial amount of information is available regarding the expressed T cell repertoire of normal strains and the role endogenous or exogenous antigens may play in modifying peripheral repertoire expression. Such information is not yet available in humans, and is a necessary adjunct to any studies seeking to identify subtle shifts in repertoire expression which may be related to pathology.

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