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T Cells in Systemic Lupus erythematosus

Systemic lupus erythematosus (SLE) is characterized by generalized autoimmunity towards many organs and involves B cell hyperactivity, autoantibody production and deposits of immune complexes in vital organs. Tolerance to antigens ceases at the onset of the disease, but the mechanisms leading to it are still unknown and may be diverse. Nonetheless, an increasing body of evidence points to the critical role of distinctive CD4⁺ T cells in driving the B cell hyperactivity responsible for autoantibody hyperproduction. Thus two main questions should be addressed to further study human SLE: the origin of the immune dysregulation which leads to the end of tolerance and the autoantigens recognized by autoreactive T cells at the onset of the disease.

For obvious reasons most of the concepts concerning immune dysregulation in SLE have been derived from the study of murine models of SLE, such as the MRL *lpr/lpr* mice. MRL mice homozygous for the *lpr* mutation (*lpr* is for lymphoproliferation) spontaneously develop a precocious SLE-like autoimmune disease with vasculitis and immune-complex glomerulonephritis and nonmalignant CD4–8– T cell proliferation. Since the autoimmune disorders are reduced by the elimination of CD4⁺ T cells by various genetic and immunological procedures, it has been concluded that CD4⁺ T cells are involved in the onset and the development of the disease [1]. The nature of the *lpr* mutation sheds light onto pathways possibly acting in SLE [2]. Indeed, the *lpr* mutation impairs the production of the Fas protein, a membrane-bound protein present on many cell types. Concerning the immune system, the Fas protein is expressed on activated T cells and, when activated by its proper ligand, initiates the signalling pathway leading to apoptosis. Thymocytes and CD4⁺ splenocytes are sensitive to Fas-induced apoptosis [3]. Unexpectedly, in spite of the absence of the Fas protein, positive and negative thymic selection is functional in MRL *lpr/lpr* mice [4]. The observed defect in the deletion of autoreactive T cells in *lpr/lpr* mice appears to occur at the periphery of the immune system [5, 6], and Fas-deficient mice are not able to negatively control

the production of autoantibodies by B cells [7]. Recently Fas mutations have been found in children presenting early signs of autoimmunity including cutaneous vasculitis, glomerulitis, thrombocytopenia, anemia and neutropenia with nonmalignant lymphoproliferative syndrome [8, 9]. In human SLE, high levels of soluble Fas have been measured, and in vitro and in vivo studies in mice have shown that soluble Fas impairs apoptosis induced by Fas ligand [10]. It thus appears that the Fas-mediated apoptosis is somehow defective in human SLE, leading to the absence of control of autoreactive B cells by CD4⁺ T cells, resulting in autoantibody production and immune-complex-mediated organ disease.

Whatever their origin may be, disorders in the cytokine production should contribute to the lymphocyte activation in SLE. Thus, in order to approach the origin of the dysregulation of the immune system observed in human SLE, the ex vivo cytokine production was analyzed in humans, but the functional properties of the lymphocytes which can be cloned and expanded in vitro may not reflect the genuine functions and properties of the populations of lymphocytes involved in vivo in the onset and progression of SLE. Nonetheless, T cells isolated from SLE patients displayed signs of activation, i.e. increased cell surface expression of MHC class II and IL-2R molecules. Increased levels of IL-2, IFN- γ and IL-6 were observed in the serum of the patients, although a similar result was not found upon in vitro stimulation of the activated T cells isolated from patients [11]. Finally, the injection of cytokines in animal models resulted in conflicting results. At this point, cytokines play important roles in B and T cell activation and tolerance, but their precise balance in vivo in relation with the onset or with the progression of SLE remains to be established [11].

The most important point concerns the nature of the antigens recognized by T cells, and which may underlie the beginning of the cascade of events leading to overt pathology. In spite of numerous attempts, the autoantigens characteristic of SLE and recognized at the onset of the disease

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by SLE-specific T cells are still unknown. Some autoantibody-inducing T cells in human lupus are activated by histone and nonhistone chromosomal proteins [12]. Another approach concerns the proper cells to study for further identification of the autoantigen they recognize. As a first step in the study of the autoantigens, the direct analysis of the T cell repertoire in patients and in mutant mice has permitted to evaluate the in vivo diversity of the T cells involved in the disease, without knowing the autoantigens they react with. If expanded, autoreactive clones could be established in vitro, the study of the autoantigen they recognize would be greatly facilitated. Such clones can be identified in mice. As an example, in MRL *lpr/lpr* mice, a very limited number of CD4+ T cell clones, defined by their V β usage and the sequence of the antigen recognition region 3 (CDR3) of the β chain, are found expanded in the peripheral blood of most animals [5]. The CDR3 sequence of the clones showed homology with the β -chain of anti-DNA-autoantibody-inducing helper T cells [13]. The elimination by the administration of antibodies or a specific lectin of this restricted CD4+ T cell population abrogates the signs of autoimmunity in MRL *lpr/lpr* mice [14, 15]. These clones are thus good

candidates for being CD4+ control T cells in murine SLE. However, none has been established in vitro so far. On the human side, there is no evidence to date of monoclonal expansions of distinctive T cell clones in SLE [16], in distinction to what has been found in some other autoimmune diseases such as multiple sclerosis [17]. The lack of results in human SLE does not, however, entirely dismiss the T cell repertoire analysis approach and rather points to the need for better defining the cohorts to be studied.

Although the etiological cause of human SLE has not yet been found, the defective CD4+ T cell control of B cell hyperactivity seems to involve the Fas pathway. Finally two important questions remain to be answered. First, what are the antigens involved in T cell activation? And secondly, is there a restricted T cell repertoire responsible for the disease as in MRL *lpr/lpr* mice, that would permit specific immunotherapy?

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