PNAS COMMENTARY

Renegade T cell clones and autoimmune disease

Harvey Cantor[a,1]

The mechanisms that normally prevent the development and expansion of self-reactive T cells from disrupting immunological tolerance and initiating various autoimmune disorders have preoccupied immunologists for decades. The study of an autoimmune disease called neuromyelitis optica (NMO) by Sagan et al. in this issue (1) is a recent example of this effort. Their overall aim is to develop a mouse model of NMO, an autoimmune disease of the central nervous system (CNS). At first glance, this would seem a straightforward problem. The principal autoantigen that serves as both a trigger and target for this autoimmune disease has been identified as aquaporin 4 (AQP4), a member of a family of water channels. Previous studies have suggested that $CD4^+$ T helper cells may induce AQP4-specific autoantibodies that cross the blood–brain barrier to inflict tissue damage that can result in paralysis and blindness. Unfortunately, a robust mouse model for this disease has been surprisingly difficult to develop. Immunization of normal mice with AQP4, or transfer of AQP4-specific T cells into adoptive hosts both fail to induce disease. In this study, Sagan et al. have used several AQP4-derived peptides that bind strongly to class II major histocompatibility complex (MHC) to carefully define a set of pathogenic T cell clones that elicit disease.

Analysis of expression of these pathogenic T cell receptors (TCRs) by $CD4^+$ T cells in normal and AQP4-deficient mice revealed that thymic deletion was incomplete and unlikely to be the sole pathway to self-tolerance. Peripheral tolerance mechanisms were then inferred from findings that transfer of AQP4-specific T cells into mice deficient in T cells developed disease, while transfer into mice containing T cells did not. These and other observations suggested that the disease-inducing ability of autoreactive AQP4-specific CD4 cells might be inhibited by regulatory T cells and that self-tolerance to the AQP4 autoantigen reflected the combined effects of thymic deletion and peripheral inhibition by regulatory T cells.

The Basis of Self-Tolerance and Autoimmune Disease

The problem of immunological tolerance as a core question in immunology became a practical problem with early studies of blood transfusion. Landsteiner's classical analyses of human erythrocyte antigens and antibodies to them led to the first general classification of blood groups and the beginning of successful human blood transfusion. Although he accounted for the failure of an individual to produce autoantibodies to autologous erythrocytes as "an absence of the immunocyte" (2, 3), the precise nature of the "immunocyte" had yet to be defined.

The subsequent definition of T and B lymphocytes expanded studies of self-tolerance from measurement of antibodies to a broader analysis of underlying cellular mechanisms. Although studies of T cell differentiation in the thymus initially suggested that deletion of autoreactive T cell clones might account for self-tolerance, improvements in technology soon revealed that thymic removal of self-reactive cells was incomplete. Autoreactive T cells were easily detectable in the peripheral lymphoid tissues of healthy individuals, humans and mice (4).

In retrospect, these findings are not surprising. Full thymic deletion of autoreactive T cell clones also narrows the T cell repertoire against potential pathogens and may impair protective immunity to infectious agents. Maintaining a full or nearly full T cell repertoire in the face of potentially lethal childhood infections has obvious evolutionary advantages over protection against autoimmune diseases, which normally occur later in life. Studies of cellular mechanisms that dampen destructive responses by autoreactive renegade T cells that have escaped thymic deletion have identified regulatory T cells as a dominant cell type with increasing clinical relevance (e.g., refs. 5 and 6).

T Helper Subsets and Autoimmune Disease

Although Sagan et al. have carefully defined the interaction between TCRs expressed by autoreactive AQP4-specific $CD4^+$ T cells and their peptide−MHC ligands, the pathogenic CD4 T cell subset(s) that drive this disease have not been clearly defined. Previously, the Th17 subset has been implicated in disease pathogenesis, possibly reflecting the ability of these cells to induce inflammatory responses that may enhance penetration of the blood–brain barrier by autoantibodies and other T cell subsets (7).

The central clinical feature of NMO (clinically termed NMOSD-NMO spectrum disorder) is the presence of circulating anti-AQP4 antibodies. Indeed, targeting B cells of NMOSD patients with monoclonal anti-CD19 or anti-CD20 has shown clear therapeutic efficacy (8). Although Th17 cells may also develop B cell helper activity (9), this is not their primary or most efficient immunological function. This specialized function is carried out mainly by T follicular helper (Tfh) cells, located mainly in the germinal center and equipped to interact with B cells (10, 11). There is increasing evidence that Tfh cells may indeed play a central role in this disease, according to analyses of NMO patients (12) and a murine model of the disease (13). The emergence of Tfh cells as a key player in this

Author affiliations: [a]Department of Cancer Immunology, Dana-Farber Cancer Institute and Department of Immunology, Harvard Medical School, Boston, MA 02215

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[1]Email: harvey_cantor@dfci.harvard.edu.

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autoantibody-mediated disorder is not surprising, given their central contribution to B cell selection, differentiation, and affinity maturation against both foreign and self-antigens and role in the loss of B cell tolerance (14, 15). Indeed, a recent analysis of the TCR repertoire of self-reactive $CD4^+$ T cells has revealed that autoreactive clones mainly express a Tfh or Tfh-like helper phenotype (16). Definition of the phenotype of AQP4-specific CD4 T cells that provoke autoantibody responses may also provide clues to the regulatory cellular interactions that inhibit their response, since self-reactive Tfh cells are regulated mainly by $CD8^+$ regulatory T cells (17–20) or follicular regulatory T cells (21, 22). These considerations also suggest that a similar Tfh:CD8 Treg interaction may regulate autoantibody responses in the subset of multiple sclerosis (MS) patients who harbor a highly active B cell component and are currently treated by plasmapheresis (23).

Although the transfer system devised by the authors does not allow direct analysis of the B cell component of this disease, the precise characterization of TCR expressed by pathogenic $CD4^+$ T cell clones defined in this report should pave the way for a clear definition of the regulatory interactions that inhibit their responses. As the authors note, "we have not created NMO in mice. However, we have provided a foundation to evaluate the regulation of AQP4-specific T cells in CNS autoimmunity." In view of its relevance to our understanding and treatment of antibody-mediated autoimmune disease, we look forward to the next chapter in the analysis of this complex and potentially devastating disease.

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