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Editorial

Understanding natural and pathological autoimmunity

The immune system is usually described as a two edged sword: it recognizes and destroys *non-self* targets protecting us against environmental pathogens, but sometimes it aims at *self* targets causing autoimmune disease. Lately, however, we have become aware of the beneficial role of autoimmunity in some biological processes such as tissue repair (Park and Barbul, 2004), which might be exploited to treat spinal cord injuries (Moalem et al., 1999), stroke (Frenkel et al., 2003) and Alzheimer's disease (AD) (Schenk et al., 1999), to mention a few examples. The use of controlled autoimmunity to treat human disorders presents us with the challenge of inducing a specific autoimmune response, strong enough to have the desired therapeutic effect but without triggering an undesired autoimmune disorder. The delicate balance separating a therapeutic immune response, such as that triggered by mucosal immunization (Faria and Weiner, 2005), from autoimmune pathology was put in evidence with the use of amyloid-beta immunization to treat AD. Early works on experimental models (Schenk, 2002), encouraged the realization of a clinical trial to test the efficacy of vaccination with amyloid-beta for the treatment of human AD. The trial, however, had to be early terminated because about 5% of the patients developed a subacute meningoencephalitis, although preliminary results suggested positive effects on the disease (Nicoll et al., 2003). The therapeutic exploitation of controlled autoimmunity is still limited by our incomplete understanding of the factors that govern pathogenic and therapeutic immunity.

In a work presented in this issue of the Journal of Neuroimmunology, Mor and Cohen report the results of their efforts trying to determine what differentiates encephalopathogenic from non-encephalopathogenic epitopes. To accomplish that aim, the authors immunized Lewis rats with a panel of 70 synthetic peptides predicted to bind MHC class II molecules and be immunogenic. Ninety seven percent of the peptides induced specific T-cell immunity, but EAE could only be triggered by active immunization or by the transfer of T-cell lines reactive with two peptides, both from synuclein beta (Mor et al., 2003). The peptides that were immunogenic but not encephalitogenic could not trigger EAE, even after the transfer of peptide-specific T cells or the administration of pertussis toxin.

The authors could not rule out the contribution of the in vivo processing of endogenous antigens–particularly within the CNS–to the encephalopathogenicity of a peptide, but they could discard many other factors: A. The *cellular localization* of the antigen; B. The *frequency* of the peptide-specific T cells; C. The *phenotype* of the peptide-specific T cells response, and D. The ability of the peptide-specific T cells to *infiltrate* the CNS (however these last two points were not exhaustively tested).

The observations made by Mor and Cohen are of importance because of what they found, and what they didn't; they tell us about the role of effector and regulatory T cells (Tregs), in determining the encephalopathogenic power of an antigen.

This work documents the existence of a large repertoire of CNS-specific T-cells in healthy rats, highlighting the compatibility of natural autoimmunity with health. How can Lewis rats be populated with CNS-reactive T-cell clones and show no signs of EAE? Self-reactive T cells and autoantibodies are also detectable in healthy humans (Lacroix-Desmazes et al., 1998; Quintana et al., 2003; Semana et al., 1999). This self-reactivity is simultaneously a source of health and disease. On the one hand, natural autoimmunity participates in several aspects of body homeostasis, including CNS repair (Schwartz and Cohen, 2000), wound healing (Park and Barbul, 2004), and the control of immune reactivity (Mimran et al., 2005), just to give a few examples. Therapeutic autoimmunity is triggered in therapies aimed to clear Alzheimer plaques (Weiner and Selkoe, 2002), speed up recovery from stroke (Frenkel et al., 2003), or to repair injured spinal cord (Moalem et al., 1999). In addition, the repertoire of natural autoimmunity of an individual can also be mined to determine the individual's susceptibility to develop an autoimmune disease (Quintana et al., 2004). On the other hand, the self-reactive clones present in the mature T cell repertoire, or at least some of them, can be activated to trigger autoimmune disease (Anderson et al., 2000). Then, what marks those clones responsible for pathologic autoimmunity?

In this respect, the value of this work might lie in what it doesn't look at. If we consider an autoimmune pathology as

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the result of a failure in the mechanisms of antigen-specific immunoregulation, we might then search the repertoire of Tregs for an explanation. Since Tregs have a TCR repertoire reactive with self-antigens (Hsieh et al., 2004), the encephalopathogenic power of a peptide might result from the strength of the antigen-specific immunoregulatory mechanisms that target it. Indeed the frequency of antigen-specific Tregs, and not of effector T cells, accounts for the differences in the susceptibility to EAE between SJL and H-2 congenic B10.S mice (Reddy et al., 2004), and between male and female B10.S mice (Reddy et al., 2005). Thus, the encephalitopathogenic power of a particular immunogen might simply reflect deficits in antigen-specific immunoregulation, "holes" in the Treg repertoire that allow the expansion of pathogenic T cell clones (Maron et al., 1999).

The therapeutic exploitation of natural autoimmunity relies on our ability to avoid the induction of undesired autoimmune disorders. Thus, we should head towards combined immunotherapies, aimed at boosting natural autoimmunity against a certain antigen, and simultaneously strengthening antigen-specific regulatory mechanisms to induce just the right kind of immune response. What makes a pathogenic epitope? How can natural autoimmunity be exploited? How can we boost antigen-specific immunoregulation? The challenge posed by these questions will certainly lead us to a deeper understanding of the behavior of the immune system and ultimately, to the development of new immunotherapies for the management of disease.

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