bristles of both brushes are facing each other. If the separation between the brushes is varied, the results will reveal how the dynamic behavior of lubricating layers is affected as the layers come into contact. The results can also show how the chain deformations can promote or hinder adhesion between the layers. Performing such experiments on biopolymers or lipids can provide information on the fluctuations of the chains within cell membranes.

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IMMUNOLOGY

Complexities in the Treatment of Autoimmune Disease

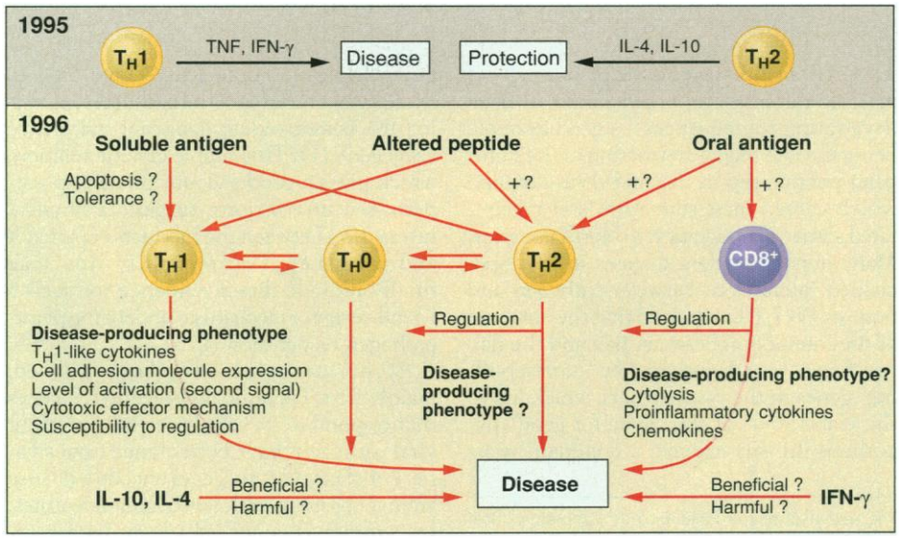
Henry F. McFarland

Two reports, one in this issue (*1*) and another in the 6 December issue (*2*), analyze a promising strategy for treatment of autoimmune diseases—administration of the offending antigen to induce tolerance. The results of both studies are troublesome—they imply that it may be problematic to apply these strategies to humans. In the report in this issue, Genain *et al.* (page 2054) (*1*) show that experimental allergic encephalomyelitis (EAE) induced in marmosets by immunization with myelin oligodendrocyte glycoprotein (MOG) can be delayed by intraperitoneal treatment with soluble MOG but that the treated animals subsequently develop a hyperacute form of disease. In the other report, Blanas *et al.* (page 1707) (*2*) noted that oral administration of large amounts of the antigen ovalbumin (OVA) may result in the generation of $CD8^+$ cytotoxic T cells and that these T cells can increase—rather than prevent—the disease process after oral administration of OVA in a murine model of insulin-dependent diabetes mellitus (IDDM). (In this model, animals are transfected with the gene for OVA on an insulin promoter to allow expression in islet cells and with an enriched population of OVA-specific $CD8^+$ T cells.) Thus, two therapeutic approaches, parental and oral administration of antigen, shown to be successful in mice and now being tried in clinical trials, may under some conditions enhance disease.

Experimental models for IDDM (the NOD mouse) and multiple sclerosis (EAE) have, in the past decade, yielded exciting advances in our understanding of the immunological mechanisms underlying experimental autoimmune disease (see figure). Both IDDM and EAE can be induced by $CD4^+$ T cells, primarily by one of the two types of helper T cell—T helper cells type 1 (T_H1), which produce proinflammatory cytokines such as interferon-γ (IFN-γ) or tumor necrosis factor–α (TNF-α). In contrast, administration or up-regulation of the T_H2-associated cytokines interleukin-4 (IL-4) and IL-10 is beneficial and can ameliorate autoimmune disease. Consequently, current concepts of autoimmune diseases focus on a disease-mediating effect of T_H1-like T cells and a protective effect of T_H2-like T cells (*3*). On the basis of this hypothesis, extensive efforts have been made to identify therapeutic strategies that tilt the T cell response toward a T_H2 phenotype. Many of these strategies—including oral administration of antigen, administration of soluble antigen without adjuvant, administration of modified antigenic peptides, or immune deviation by T_H2-associated cytokines—work in mouse models and are currently in various stages of clinical testing for several autoimmune diseases. Now several recent studies, including the new report by Genain *et al.* (*1*), suggest that the distinction between disease-producing T_H1 T cells and protective T_H2 T cells is overly simplistic and that the relation of proinflammatory and T_H2-associated cytokines in autoimmune disease is extremely complex. For example IL-10 contributes to, or increases, disease in the NOD model (*4*). IL-4, the prototypic T_H2-associated cytokine, can augment autoimmune uveitis in rats (*5*), and T_H2 T cells failed to suppress IDDM in the NOD mouse (*6*). Furthermore, the study by Blanas *et al.* (*2*) raises the possibility that in addition to $CD4^+$ T_H1 T cells, $CD8^+$ T cells may also contribute significantly to some autoimmune diseases. These findings contrast with previous suggestions that oral administration of antigen induces a population of $CD8^+$ T cells that suppress disease (*7*).

The observations in the two new reports must be viewed with some caution. Genain *et al.* speculate that the hyperacute disease was due to the induction of T_H2-like T cells, resulting in an increased antibody response to the antigen. And in fact previous studies in rodents and later in the marmoset have shown that antibody to MOG, which is on the surface of myelin, can enhance demyelination and increase disease (*8*).

However, a number of questions remain unresolved. For example, the authors speculate that residual T_H1-like T cells were responsible for lesion initiation. Could the T_H2-like



Growing complexity.

The author is in the Neuroimmunology Branch of the National Institutes of Health, Bethesda, MD 20892, USA. E-mail: henrymcf@helix.nih.gov

T cells have been directly involved in disease induction? Also, the distinction between T_H1 and T_H2-like T cells is less clear in humans than in mice; a substantial number of human myelin basic protein–specific T cells have a T_H0 phenotype, and the minority have a T_H1 phenotype (9). Thus, further definition of these populations in the marmoset will be necessary before the findings of Genain *et al.* can be fully understood. The investigators report changes in IL-10, but the cytokine most consistently associated with a T_H2-like phenotype in humans, IL-4, was not examined. Thus, it is possible that in the marmoset a T cell subset intermediate between T_H1 and T_H2, a T_H0 T cell, could mediate disease, as has been shown in the mouse EAE model (*10*).

The possibility that these findings are unique for MOG also needs consideration. Antibodies to other myelin antigens such as myelin basic protein or proteolipid protein, which have been the primary focus of emerging therapies, may have less influence on disease course, but even this is uncertain.

Finally, the potential of a $CD8^+$ T cell population to mediate disease must be considered: $CD8^+$ T cells specific for various myelin antigens have been found (*11*). The results of Blanas *et al.* (*2*) raise the possibility that a $CD8^+$ T cell population can be generated after oral administration of antigen and can mediate disease. But it is unclear how accurately results from a highly artificial animal model can be extrapolated to human disease. As the authors indicate, some questions remain puzzling in their model. For example, why does oral administration of antigen in animals expressing OVA on the insulin promoter fail to provoke disease?

Another area of concern is that T_H1-like T cells, although certainly linked to disease production, may be only one component of the immunological attack. Antibody can exacerbate EAE, so if a treatment only partially reduces the T_H1 response but augments the T_H2 response and increases antibody to an organ-specific autoantigen, the disease can get worse. Also, the role of $CD8^+$ T cells in autoimmune diseases is poorly defined. Although $CD4^+$ T cells may have a major role in the initial induction of many autoimmune diseases, $CD8^+$ T cells, which are cytotoxic and can secrete proinflammatory cytokines and chemokines, may also contribute to tissue damage (*10*).

Despite these reservations, these findings and others reported previously underscore the fact that the role of cytokines in immune regulation and disease is extremely complicated (see figure) and may depend on the timing of the treatment and on the dose. For example, increased concentrations of cytokines such as IL-10 at the initiation of autoimmune disease may enhance the disease process through mechanisms such as up-regulation of major histocompatability complex expression. In contrast, when IL-10 is administered after disease is initiated, the predominant effect may be to inhibit T_H1-like responses and functions. An example of these complexities is IFN-γ. Although IFN-γ is thought to be the prototypic T_H1 cytokine, IFN-γ has some protective properties in the EAE model (*12*). In contrast, administration of IFN-γ to patients with multiple sclerosis seems to increase disease (*13*).

Mechanisms of autoimmunity are more complicated than a simple T_H1-T_H2 dichotomy would suggest. More important, as we move into the clinic to treat chronic diseases with treatments that are effective in some animal models, clinicians must carefully monitor the effect of these treatments. The potential for obtaining results different from those predicted from experiments in animals or in vitro is great.

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BOTANY

A Ligand-Receptor Mechanism in Plant-Pathogen Recognition

Chris Lamb

Losses from disease limit the productivity of agricultural crops, and epidemics can have devastating consequences—a good example being the late blight destruction of the European potato crop in the mid–19th century, which caused mass starvation and precipitated a wave of emigration to North America. Many important plant diseases involve specialized interactions between pathogen and host. In 1947, Flor reported that the outcome of the interaction between flax and the flax rust fungus was determined by "corresponding" genes in the two partners, which led to the elaboration of the "gene-for-gene" hypothesis. In this scheme, a dominant resistance (*R*) gene confers resistance only to those races or strains of the pathogen expressing the corresponding dominant avirulence (*avr*) gene (*1*). This simple genetic relation, which gives a good account of many plant-pathogen interactions, suggests a physical interaction between the products of paired *R* and *avr* genes. Two reports in this issue finally provide direct evidence for such a ligand-receptor mechanism underlying plant-pathogen recognition (*2*, *3*).

Many *avr* genes have been isolated, mainly from bacteria, and recently *R* genes that respond to specific bacterial, fungal, or viral pathogens have been cloned from a variety of plants (*1*). *avr* genes encode a diverse group of proteins with few common features. In contrast, *R* genes, which mediate resistance to diverse pathogens, share common structural elements suggestive of a signal transduction function. Indeed, activation of *R* gene products induce the hypersensitive resistance response (*1*), a battery of protective mechanisms, and rapid death of challenged host cells. Thus, *Pto*, which conditions resistance of tomato to bacterial speck disease caused by the *Pseudomonas syringae* pathovar *tomato* and was the first *R* gene isolated, encodes a cytoplasmic protein–serine-threonine kinase, and other *R* genes encode proteins with leucine-rich repeats, often implicated in protein-protein interactions, and in some cases with nucleotide binding sites. Interestingly, the rice *Xa21* gene, which confers resistance to a pathogenic Xanthomonad, encodes a receptor-like kinase with a putative extracellular leucine-rich repeat and intracellular catalytic domains connected by a short transmembrane region (*4*).

Although such a protein has obvious structural attributes for interaction with signals external to the cell, it was unclear how bacterial *R* genes encoding cytoplasmic proteins might function in the recognition of extracellular pathogens. A clue came with the realization that the *Hrp* (*hypersensitive response and pathogenicity*) gene cluster in many phytopathogenic bacteria encodes proteins

The author is at the Plant Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA. E-mail: lamb@salk.edu