Commentary

Relationships among Antigen Presentation, Cytokines, Immune Deviation, and Autoimmune Disease

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In this issue, Saoudi and colleagues expand on their previous observation that development of experimental allergic encephalitis (EAE) can be suppressed by preimmunizing rats with a myelin basic protein (MBP)–derived peptide that has been coupled to an anti-IgD antibody (1, 2). Their observations illustrate how antigen presentation by a particular cell type can induce a form of tolerance, immune deviation, in which autoimmune responses are channeled in a harmless direction. Types of T cell tolerance include (*a*) death of T cells that are specific for a particular MHC–peptide combination (clonal deletion); (*b*) T cell survival in a form that is unresponsive or hyporesponsive to activating stimuli (anergy); and (*c*) T cell survival in a form that responds strongly to a particular stimulus, but in a way that differs from the standard response (immune deviation). Although clonal deletion and anergy might seem to be the most complete forms of tolerance, they may be limited by thymic replacement of deleted or anergic antigen-specific T cells. Immune deviation, on the other hand, can be self-perpetuating because cytokine responses of fully differentiated T cells can influence the differentiation of newly generated, antigen-stimulated T cells.

Immune deviation was first described in the 1960s (3), but mechanistic understanding of the process was limited before the description of $CD4^+$ T cell subsets that can be distinguished by the cytokines they produce (4, 5). $CD4^+$ T cells can be characterized as Th1 cells, which secrete IL-2, lymphotoxin (TNF-β), and IFN-γ, but not IL-4, IL-5, IL-9, IL-10, or IL-13, and Th2 cells that secrete the opposite set of cytokines. Cytokine responses that resemble Th1 or Th2 responses, but are not necessarily made by $CD4^+$ T cells, are referred to as type 1 or type 2, respectively. Type 1 responses are generally associated with cytotoxic effects (CTL, activated macrophages that kill ingested microbes, complement-fixing antibody), while type 2 responses are associated with non–complement-fixing antibody and allergy-related phenomena (eosinophilia, mucosal mastocytosis, IgE) (4–6). Although individual T cells or T cell clones can secrete other combinations of cytokines (7), $CD4^+$ T cell responses in disease states often are predominantly Th1-or Th2-like (8, 9).

$CD4^+$ T cells often pass through a "Th0" stage of differentiation in which they secrete both type 1 and type 2 cytokines (10). Although cytokine responses can remain mixed, the same $CD4^+$ T cells can be induced to secrete either type 1 or type 2 cytokines, depending on the environment in which they are activated. Several factors may influence T cell differentiation.

Cytokine Influences. IL-12, IFN-γ, IFN-α, and IFN-β all promote the secretion of IFN-γ and inhibit type 2 cytokine secretion (with the exception that IL-12 stimulates IL-10 secretion) (11–13). IFN-γ itself inhibits type 2 cytokine secretion and contributes to the anti-type 2 effect of IL-12. IL-4 stimulates $CD4^+$ T cells to differentiate into cells that secrete IL-4 and other type 2 cytokines, and it inhibits type 1 cytokine secretion by differentiating $CD4^+$ T cells (14). If IL-4 priming is essential for the generation of an IL-4 response by most naive T cells, IL-4 might initially be produced by basophils and/or an $NK1^+$ T cell subset that expresses this cytokine without priming (15, 16). Alternatively, other factors may substitute for IL-4 in the stimulation of a Th2 response. Two additional cytokines have more complex effects on the immune system. IL-10 inhibits macrophage antigen presentation (17) but has more of an inhibitory effect on Th1 responses than on Th2 responses, possibly because it suppresses macrophage IL-12 secretion and NK cell IFN-γ secretion (18). TGF-β suppresses the development of both Th1- and Th2-related effector responses and appears to ultimately promote the development of a type 1 or type 2 response in different situations (19–21).

Costimulatory Molecules. Interactions between the B7s on APCs and CD28 or CTLA4 on differentiating naive T cells are important for induction of both allergy-related responses (IgE, eosinophilia) (22) and for cell-mediated immunity (graft rejection) (23). There is no convincing evidence that reagents that block such costimulatory interactions modulate a developing response in either a type 1 or type 2 direction (24). Selective B7-1 or B7-2 costimulation predisposes to type 1 or type 2 cytokine responses, respectively, in some models (25), while in other models, either B7-1 or B7-2 costimulation can induce a type 1 or a type 2 response (reference 26, and Gause, W. C., personal communication).

Type of APC. No independent relationship between type of APC and cytokine response has been definitively established. Mice immunized with antigen-pulsed splenic dendritic cells or activated B cells were reported to generate both IgG1 and IgG2a responses, while immunization with antigen-pulsed peritoneal macrophages only generated IgG1 responses (27). These results suggest that antigen presentation by dendritic cells or B cells might be more likely to stimulate IFN-γ production, which enhances IgG2a responses (6), than would antigen presentation by peritoneal macrophages. In contrast, mice immunized with antibodies that are focused onto B cells (anti-IgD), macrophages (anti-CD11b), or dendritic cells (ag-

gregated mAb 33D1) all generate predominantly IgG1 responses (Finkelman, F., unpublished data), and macrophages, dendritic cells, and B cells can all induce either a Th1 or a Th2 response, given the proper cytokine environment (28).

Site of Antigen Presentation. Inhaled OVA has a greater propensity than parenterally injected OVA to stimulate a Th2 response (29). When administered orally, antigens that stimulate a strong systemic antibody response can induce tolerance that is associated with T cell production of TGF-β (30). These results may reflect unique populations of T cells or APCs in the lung or gut, the influence of cytokines that are expressed at these sites, or other uncharacterized factors.

Polarized Cytokine Production in Disease States. Specific cytokine patterns are associated with cure or exacerbation of both infectious and immune-mediated diseases. Intracellular protozoan infections are limited by IFN-γ but exacerbated by IL-4, while some gastrointestinal nematode infections are controlled by IL-4 and exacerbated by IFN-γ (8, 9). Atopic allergy is mediated by type 2 cytokines (4). In addition, graft vs host disease (GVHD) that is characterized by a systemic lupus erythematosus-like autoimmune syndrome is associated with type 2 cytokine production and is inhibited by anti–IL-4 antibody (31). On the other hand, type 1 cytokines are produced in acute GVHD, in which donor $CD8^+$ T cells develop into CTL that destroy the host immune and hematopoietic systems. Treatment with anti–IFN-γ or anti-TNF mAb ameliorates disease, and treatment with anti–IL-2 mAb converts acute GVHD to autoimmune GVHD (reference 32, and Via, C. S., and F. D. Finkelman, manuscript in preparation). Th1 responses are also critical for the development of insulin-dependent diabetes mellitus in nonobese diabetic mice and EAE in mice and rats (33). Both disorders can be ameliorated by treating mice with IL-4 before the development of clinically apparent disease (34, 35), and the development of diabetes mellitus can be prevented by treating mice with anti–IFN-γ mAb (36). EAE association with type 1 cytokines may relate more to the effects of TNF than IFN-γ, in that anti-TNF mAb ameliorates disease, while anti-IFN-γ mAb can actually exacerbate disease (37, 38).

Association of specific immune-mediated disorders with cytokine patterns raises the possibility that immunization with a disease-related antigen in a way that would promote the development of an opposing set of cytokines might prevent disease development. Mason and colleagues applied this strategy to prevent the development of EAE by immunizing rats with an anti-IgD mAb conjugated to a peptide that is a major T cell epitope of MBP (1, 2). Injection of this conjugate both focuses the MBP-derived peptide onto $mIgD^+$ B cells, which provides a large population of cells capable of presenting the antigen to MBP peptide–specific T cells, and it activates B cells, making them capable of presenting antigen in a manner that causes T cell activation rather than tolerance (39). Consistent with a previous study in which antigen presentation by anti-IgD antibody–activated B cells stimulated a predominantly Th2 response (40), the cytokine response made by MBP-specific T cells that were primed with the anti-IgD mAb-MBP peptide conjugate before challenge with MBP in CFA was deviated in the Th2 direction (more IL-4, less IFN-γ), as compared to that generated by T cells from unprimed mice injected with MBP in CFA. It remains to be established, however, that antigen presentation by B cells, as opposed to antigen presentation by any cell type in the absence of CFA, is responsible for immune deviation in the EAE system.

Use of Immune Deviation for Treatment of Immune-mediated Disorders. The deviation of established cytokine responses is difficult but not impossible. "Desensitization" to grass pollen can be associated with an increase in the IFN-γ:IL-4 response to the allergen (41); mice immunized once with irradiated *Schistosoma mansoni* cercariae develop a predominantly Th1 response, while repeated immunization with the same parasite causes the response to become predominantly Th2 (42); IL-12 treatment starting at the time of inoculation of mice with *Heligmosomoides polygyrus* causes the secretion of Th1-associated cytokines rather than the usual Th2 response; however, the response switches to Th2 once the IL-12 treatment is discontinued (43). It is not known if any of these phenomena involve the actual switching of cytokine production by partially or fully differentiated T cells or the replacement of one T cell population by another. The clinical responses of some rheumatoid arthritis and multiple sclerosis patients to orally administered type II collagen or MBP, respectively, may represent the successful application of immune deviation to human diseases (30). It remains to be determined whether immunization with antigens targeted to APCs may allow some immune-mediated disorders to be treated in a practical and effective manner.

The use of immune deviation as therapy carries potential risks as well as benefits. For example, IL-12 treatment of mice that would normally develop autoimmune GVHD prevents the development of this disorder but causes instead the development of acute GVHD (44). Further understanding of stimuli that induce or suppress T cell expression of specific cytokines and of the roles of specific cytokines in disease pathogenesis will facilitate the use of this double-edged sword in the safest manner possible.

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