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## IMMUNOREGULATION BY HELPER T CELL SUBSETS

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It is now widely accepted that most established clones of mouse helper T (Th) cells belong to one of two subsets, termed Th1 and Th2, distinguished by different patterns of lymphokine expression when activated (1). IL-2, IFN- $\gamma$  and lymphotoxin are produced exclusively by the Th1 subset of clones, whereas IL-4 and IL-5 are produced only by Th2 clones. Both subsets can act as helpers for B cell activation in vitro, under certain conditions, however, Th2 clones are generally more effective helpers. The two most significant functional distinctions are: (a) only Th1 clones can transfer delayed-type hypersensitivity (DTH) (2) and (b) only Th2 clones can induce an IgE antibody response (3).

Recent studies of IL-2, IL-4 and IFN- $\gamma$  expression in human Th clones suggest that all possible patterns of expression are possible, although the frequency with which certain patterns occur is substantially altered in some disease states (4). Despite these apparent differences between mouse and human Th cells, the roles played by IL-4 and IFN- $\gamma$  in IgE expression are similar in both species. Thus, only human Th clones which express IL-4, but little or no IFN- $\gamma$  stimulate IgE responses (4). Unfortunately, the lymphokine expression pattern of Th cells that mediate DTH in man is not yet known.

Analysis of the immune response to parasites in both rodents and humans provides strong evidence for the existence of two distinct patterns of lymphokine

production in vivo. For example, mice respond to infection by many helminth parasites with T cell-dependent increases in eosinophils and mucosal mast cells and prominent IgE responses. In vitro, IL-4 is required for IgE production, IL-5 is the most potent and specific T cell-derived eosinophil growth and differentiation factor, and mucosal mast cells grow optimally in a mixture of IL-3 and IL-4. This leads to the prediction that Th2, but not Th1, cells regulate these characteristic responses to helminth infections. The roles of IL-4 in IgE production and IL-5 in eosinophilia have now been confirmed in vivo, suggesting that this interpretation is correct. For simplicity, we refer to this as the "Th2 pathway". The fact that eosinophilia usually accompanies high IgE responses, in such diverse disease states as atopy, helminth infection and Hyper-IgE syndrome, is evidence for the existence of a distinct "Th2 pathway" in man, even though the cellular basis for it is not yet clear.

A better example of the different consequences of responses dominated by either the "Th1" or "Th2 pathway" comes from studies of Leishmania major infection in inbred strains of mice. Subcutaneous infection of resistant strains, such as C3H or C57BL/6, with L. major results in a localized lesion which heals spontaneously. This infection generates a strong DTH response but very little antibody. The key component of the healing response appears to be induction of the microbicidal activity of infected macrophages by IFN- $\gamma$ . This suggests that the response of resistant strains is dominated by the "Th1 pathway". Direct support for this comes from the observation that spleen cells of infected, resistant mice contain large amounts of IFN- $\gamma$  mRNA but very little IL-4 mRNA (5), and from

the ability of a L. major-specific Th1 line to transfer resistance to BALB/c mice (6). Based largely on the known in vitro activities of the lymphokines produced by Th1 clones, the "Th1 pathway" should efficiently activate cytotoxic activities of macrophages and NK cells, stimulate expression of complement-fixing IgG2a antibodies and of the Fc receptors with which macrophages and NK cells bind IgG2a, and mediate direct cytotoxic effects via IFN- $\gamma$  and lymphotoxin.

In contrast, infected BALB/c mice do not develop DTH, are unable to control the infection and ultimately die of visceral leishmaniasis. They do, however, produce significant antibody responses and substantially elevated IgE levels. The suggestion that this represents a response primarily of the "Th2 pathway" is consistent with the high levels of IL-4 mRNA and low levels of IFN- $\gamma$  mRNA found in infected BALB/c spleen cells (5) and with the ability of Th2 lines to accelerate the disease (6). Several manipulations, such as depletion of T cells with sublethal irradiation or anti-L3T4, can convert confer resistance upon BALB/c mice and, in doing so, change the pattern of responses and lymphokines from predominantly Th2 to Th1.

Humans infected with L. donovani (kala-azar) display a similar spectrum of immune responses. Many people develop strong cell-mediated responses, but little or no antibody, heal quickly, and become resistant to further infection (7). Others develop visceral disease, characterized by high antibody levels, no cell-mediated immunity and no effective control of the infection. This again suggests that these two major patterns of Th response exist in man and they have a reciprocal relationship in both man and mouse.

A number of important questions remain before the

significance of this level of immune regulation is fully understood::

1. What is the cellular origin of these 2 patterns of lymphokine expression? Do Th1 and Th2 leave the thymus as distinct cell lineages in mouse? If so, what are their counterparts in man? If not, are Th cells bipotential cells that can differentiate, upon activation, to one expression pattern?
2. What are the conditions that lead to the preferential expression of one pattern of lymphokine expression?
3. Are all of the lymphokines of one pattern coordinately regulated or can some be differentially expressed relative to others?
4. What other disease states result from differences in the expression of one or both pathways?
5. Can the activation of these 2 pathways be manipulated either to optimize protective immunization or to alter the course of an established disease?

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