Development of helper T cell subsets: a central role for interleukin 12

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The immune response pattern elicited during an infection depends on the type of causative agent. Humoral immunity restricts the harmful effects of extracellular microorganisms and soluble toxins, while a cell-mediated immune response controls the spread of intracellular pathogens. Generation of the appropriate immune effector mechanisms is regulated by the pattern of cytokines released by CD4+ helper T (T_H) cells. They can be classified into two subsets: T_H1 cells give rise to cell-mediated immunity and are characterized by the production of interleukin 2 (IL-2) and gamma-interferon (IFN-γ), whereas T_H2 cells are more efficient in mediating antibody formation and secrete IL-4, IL-5, IL-6 and IL-10 (Refs 1, 2).

Depending on the stage and the site of infection as well as the genetic background of the host, pathogens trigger polarized T_H responses[3]. Many bacteria, protozoa and viruses stimulate T_H1 cells, whereas helminths preferentially induce T_H2 cells. In murine models of malaria and schistosomiasis, consecutive activation of CD4+ T cell subsets has been observed; and in experimental leishmaniasis, mice of resistant strains develop a T_H1 response, whereas susceptible mice display a T_H2-like cytokine secretion pattern.

Because the type of T_H response induced may determine the outcome of an infection, by favoring either control of the pathogen or promotion of disease, understanding the mechanisms that direct the differentiation of T cell subsets is of considerable importance. There are several alternative, although not necessarily mutually exclusive, possibilities.

First, different types of antigen-presenting cells (macrophages, B cells or dendritic cells), delivering distinct co-stimulatory signals, may favor the expression of different sets of cytokines. In agreement with this hypothesis, it has been suggested that macrophages are required for generation of T_H1 cells, whereas antigen presentation by B cells induces T_H2-like cells[4].

Second, the features of the antigen may have a deterministic role. In experimental leishmaniasis, studies with T_H1 or T_H2 cell lines that have either a protective or an exacerbative effect, respectively, have shown that they respond to different pools of parasite antigens[5].

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Third, differences in the density of the T cell receptor ligand on the antigen-presenting cell surface may affect the type of developing T_H cell[6].

Finally, lymphokines themselves may regulate the pattern of lymphokines produced by antigen-stimulated CD4+ T cells. The presence of IL-4 or IL-10 promotes the development of T_H2 cells or inhibits T_H1 formation, respectively, whereas IFN-γ enhances the generation of T_H1 cells and suppresses proliferation of T_H2 cells[7–9]. Thus, T_H1 cells and T_H2 cells crossregulate each other by self-stimulation and/or mutual inhibition, thereby creating a reciprocal relationship. However, what is the origin of such signals during primary T cell activation in the early phase of the host's interaction with a pathogen?

Recently, a study by Hsieh *et al.*[10] has shed light on these processes. To examine antigen-dependent priming and short-term differentiation of T cells, the authors used an *in vitro* system in which uniformly naive CD4+ T cells are derived from a transgenic mouse line that expresses only a T cell receptor specific for ovalbumin. The presence of *Listeria monocytogenes* during *in vitro* priming with ovalbumin induced the development of T_H1 cells, as characterized by secretion of IFN-γ. This

effect on T cells involved an interaction between *Listeria* and macrophages that resulted in production of IL-12. Thus, IL-12 appears to act directly on naive CD4+ T cells to promote T_H1 development and initiation of cell-mediated immunity. It therefore represents the counterpart of IL-4, which directly induces the generation of T_H2 cells. In the presence of both IL-4 and IL-12, however, IL-4 was shown to be dominant because it decreased the level of IL-12-stimulated IFN-γ production[10].

In addition, IL-12 seems to be important for the development of natural immunity. In mice with the severe combined immunodeficiency (SCID) mutation, which lack T and B cells, *Listeria*-stimulated IL-12 induces IFN-γ production by natural killer (NK) cells[11]. IL-2 acts synergistically with IL-12 to augment IFN-γ release by NK cells as well as CD4+ T cells[11,12]. On the other hand, tumor necrosis factor α (TNF-α) is required as a cofactor for the effect of IL-12 on NK cells but not on naive T cells[10,11]. Thus, IL-12-dependent activation of NK cells and T cells may be regulated differently.

Interestingly, the inhibitory effect of IL-10 on T_H1 development[7] may be explained by its ability to block IL-12 production[10]. Because both cytokines are produced by macrophages, the commitment of CD4+ cells towards the T_H1 lineage appears to be regulated by both inhibitory and stimulatory cytokines released by innate immune cells before the development of specific immunity.

It is conceivable that certain pathogens or host factors may favor the production of IL-12, resulting in preferential development of T_H1 cells and induction of cell-mediated immunity rather than a humoral immune response. In murine cutaneous leishmaniasis, genetically resistant mice were found to have a greater capacity for IL-12 release than genetically susceptible mice[13]. However, in the initial phase of infection (2 d), both resistant *and* susceptible mice produced significant levels of IL-12 (Ref. 14). This is in accord with the above suggestion that the type of developing T_H cell is also influenced by the presence of inhibitory factors in the microenvironment.

Probably the most important implication of the findings of Hsieh *et al.* is the possibility of using IL-12 for designing immunotherapeutic agents or vaccines against infectious diseases. Towards this goal, encouraging results have been obtained in the experimental *Leishmania* model[13,15]. Administration of IL-12 during the first week of infection with *Leishmania major* resulted in the cure of normally susceptible mice and provided resistance against reinfection. These protective effects were associated with an increase in antigen-stimulated IFN-γ release and a markedly decreased production of IL-4, i.e. a reversal of T_H1 and T_H2 activities.

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