IL-12: Initiation Cytokine for Cell-Mediated Immunity

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From the time of Jenner's first cowpox inoculations until the most recent vaccine trials for human immunodeficiency virus (HIV), immunization has been an empirical science. In spite of the large body of accumulated knowledge about mechanisms of immunity, the ability to induce a specific type of immune response remains more art than science. Advances of the last few years, however, promise to initiate a new era in vaccine development. We now know that T lymphocytes, which are required for both cell-mediated immune responses and the production of antibody by B lymphocytes, are composed of two distinct subsets—T helper 1 (T_H1) and T helper 2 (T_H2) cells (*1*). T_H1 cells produce interleukin-2 (IL-2) and interferon-γ (IFN-γ) and execute cell-mediated immune responses (delayed hypersensitivity and macrophage activation); whereas T_H2 cells produce IL-4, IL-5, and IL-10 and assist in antibody production for humoral immunity. This paradigm has been and continues to be a powerful driving force in the field of immunology (*2*). However, the mechanisms by which a particular T cell lineage is steered down the path toward a T_H1 or T_H2 fate have remained unclear. In this issue of *Science*, Hsieh and colleagues (page 547) demonstrate that interleukin-12 (IL-12), a recently described cytokine that stimulates IFN-γ production (*3*), induces the differentiation of T_H1 cells from an uncommitted T cell and, consequently, initiates cell-mediated immunity. We can now rationally design vaccines for those diseases that are best controlled by cell-mediated immunity.

The immune system uses many mechanisms for attacking pathogens, but not all of these are activated after either infection or immunization. Many bacterial, protozoal, and viral infections trigger a cell-mediated immune response, while other pathogens, such as helminths, primarily induce an antibody response (*4*) (Fig. 1). Preferential development of one T helper cell subset is often apparent at the early stages of an infection, suggesting that the mechanisms that drive the immune response in one direction or the other operate soon after exposure to antigen. Several factors influence the development of T helper cell subsets, but the most important may be the early exposure to cytokines. The decisive role of cytokines in T cell differentiation is best exemplified in cutaneous leishmaniasis, a disease caused by a parasitic protozoan. Experimental *Leishmania major* infections in different mouse strains induce either a T_H1 or a T_H2 response. If T_H1 cells are induced, the animal lives; if T_H2 cells are induced, it dies (*5*). In vivo depletion of IFN-γ with monoclonal antibodies ablates T_H1 cell development and promotes T_H2 cell differentiation, while IL-4 depletion inhibits T_H2 expansion, leading to T_H1 cell development (*6*). IL-4 promotes T_H2 cell development in vitro as well (*7*). Although IFN-γ augments T_H1 cell expansion and may be required for T_H1 cell differentiation, it is nevertheless not in itself sufficient to bias the immune response towards T_H1 cell development, and other cytokines may be required (*8*).

IL-12, originally called natural killer cell stimulatory factor, is a logical candidate for participation in the differentiation of T_H1 cells. IL-12 is produced by macrophages and B lymphocytes, and stimulates the production of IFN-γ from T cells and natural killer cells (*9,10*). Furthermore, IL-12 enhances the expansion of human T_H1 cells in vitro (*11*). However, in order to determine directly whether IL-12 initiates T_H1 cell differentiation after exposure to antigen, a population of naïve T cells is required. To accomplish this, Hsieh and colleagues took advantage of the fact that CD4+ T cells derived from T cell receptor transgenic mice only express the transgenic T cell receptor, in this case a T cell receptor that recognizes ovalbumin. Because these mice had not been previously exposed to ovalbumin, all of their CD4+ T cells were naïve, providing a system in which differentiation into T_H1 or T_H2 cells after antigenic stimulation could be studied. Using this approach, Hsieh and colleagues and Seder and colleagues confirmed earlier studies indicating that IL-4 drives the differentiation of T cells towards the T_H2 type (*8*). Now Hsieh and colleagues demonstrate that IL-12 acts in an opposite manner and drives the lineage toward T_H1 cell development (Fig. 1). Furthermore, they link the capacity of *Listeria* to induce a T_H1 cell response with its ability to stimulate IL-12 production (Fig. 2). Thus, *Listeria*-infected macrophages also stimulate T_H1 cell differentiation in this system, a process that was inhibited when IL-12 was depleted with antiserum to IL-12. Thus, certain pathogens may preferentially induce cell-mediated immunity because they can stimulate IL-12 production. Indeed, the ability of several other pathogens or their products, including lipopolysaccharide from Gram-negative bacteria, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, and *L. major*, to induce a T_H1 response correlates with their capacity to stimulate the production of IL-12 (*9,12,13*). Taken together, these data indicate that a central component of T_H1 cell development in response to infection may be the stimulation by the pathogen of IL-12 producing cells, such as macrophages (Fig. 1).

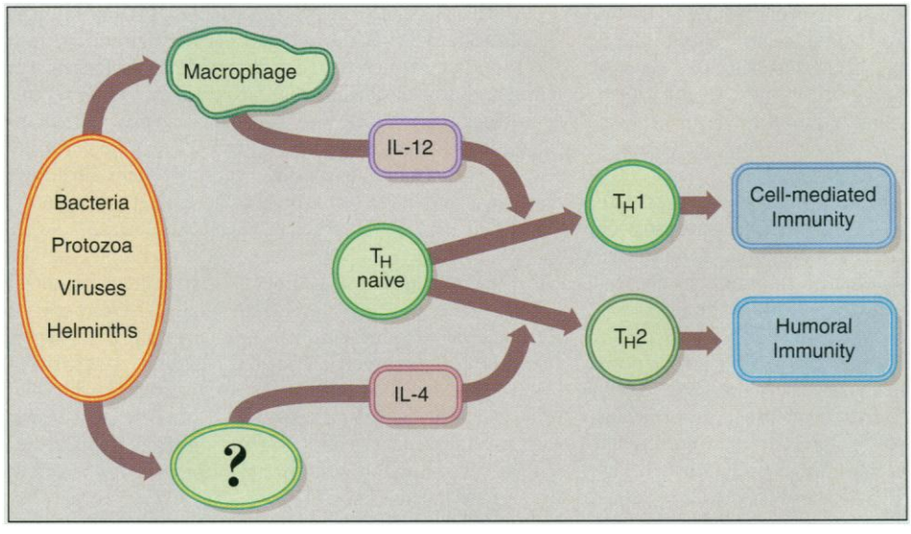

Fig. 1. Cytokine-driven T helper cell differentiation. Several bacteria and protozoa (and likely some viruses) stimulate the production of IL-12 by macrophages or other cells. IL-12 then directs the differentiation of naïve T cells toward the T_H1 subset, which control cell-mediated immunity. Other pathogens, particularly helminths, stimulate IL-4 production, which drives naïve T cells in the T_H2 direction. T_H2 cells primarily mediate help for antibody production. The characteristics of the pathogen that determine which pathway will dominate are unknown.

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Because the clever technical approach used by Hsieh and colleagues cannot be applied in humans, it is difficult to address the role of IL-12 in human T cell development. Nevertheless, recent studies by Manetti and colleagues (9) indicate that IL-12 may have a similar role in the differentiation of T cell subsets in man. Although diseases are often associated with a dominant T helper cell phenotype, as discussed above, T cells taken from patients include a mixture of T_H1 and T_H2 cells, as well as T helper cell subsets with other cytokine patterns. Manetti and colleagues (*11*) found that such a mixed T cell population from patients with allergies could be shifted from the normally dominant T_H2 phenotype toward an experimentally induced T_H1 phenotype by the addition of IL-12. One implication of these results is that IL-12 may have therapeutic applications in a wide range of diseases. IL-12 might be useful in the treatment of allergies, in which an inappropriate T_H2 immune response mediates immunopathology, as well as infections and malignancies that could best be controlled by cell-mediated immunity. IL-12 might make a particularly important contribution in HIV infection, which is associated with a progressive loss of T_H1 cells, decreased natural killer cell function, and a corresponding increase in T_H2 cells (*14*). IL-12 significantly enhances the cytotoxic function of natural killer cells from HIV-infected patients (*15*) and may also be able to enhance T_H1 cell function, although it is not clear whether this would have a therapeutic effect against the virus. It is encouraging that, in immunodeficient mice, IL-12 induction of natural killer cells can protect against *T. gondii*, a major opportunistic infection in patients with acquired immunodeficiency syndrome (*13*).

Cytokines also provide inhibitory signals for T cell subset differentiation. As reported by Hsieh and colleagues, IL-4 itself appears to inhibit the ability of IL-12 to promote T_H1 cell development, possibly by providing a more powerful stimulus for T_H2 cell development than IL-12 provides for T_H1 cell development. Furthermore, both IL-4 and IL-10 can inhibit IL-12 production by human monocytes (*16*). Similarly, in the T cell receptor transgenic system, IL-10 inhibited the ability of *Listeria*-infected macrophages to drive T_H1 cell differentiation, probably by decreasing IL-12 production. Because IL-10 is produced by macrophages, macrophages either augment or inhibit T_H1 cell development, depending upon the relative amounts of IL-12 and IL-10 produced by these cells.

The implication of these studies is clear: IL-12 is a critical component in the development of cell-mediated immunity. This information can be directly applied to vaccine development against diseases known to be controlled by cell-mediated immunity. In such vaccines, IL-12 might be included as an adjuvant. In fact, the efficacy of adjuvants incorporating bacteria or their products may be related directly to their ability to induce IL-12 production. Whether this is the case or not, the recognition that cytokines generated by cells without antigen specificity are the principal signals for T helper cell subset differentiation is of major importance. This knowledge will become even more powerful when we succeed in identifying the source of the IL-4 that drives T_H2 cell differentiation (possibly mast cells, basophils, or T cells); in defining the factors responsible for the induction of cytokines, such as IL-10, which inhibit T_H1 cell differentiation; and in determining the molecular mechanism by which particular pathogens stimulate IL-12 or IL-4 production. The recent rapid advances in this field suggest that we will soon be able to apply our understanding of T helper cell subset selection to improved immunotherapy and vaccines.

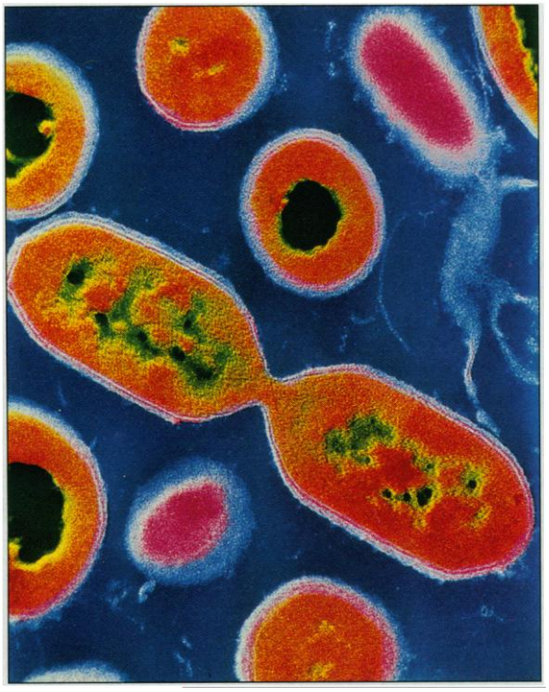

Fig. 2. The bacterium *Listeria*. *Listeria* induces a T_H1 cell response by triggering IL-12 secretion from macrophages. Magnification: ×27,000. [Image: CNRI/Science Photo Library/Photo Researchers]

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