Cytokine Patterns During the Progression to AIDS

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During infection by human immunodeficiency virus (HIV), the virus replicates in cells of the immune system (*1*). T lymphocytes expressing CD4 are preferred targets, and this subset of cells is eventually severely reduced, resulting in deficient immune responses. HIV preferentially infects activated T cells, precisely the T cells that respond to and protect against environmental pathogens. This selective loss may explain why patients with AIDS can no longer fight common pathogens and have frequent infections. This degeneration of the immune system is not prevented by a strong antibody response against HIV, and in fact HIV-infected patients normally have high concentrations of antibodies to HIV in their blood (which are used to diagnose HIV infection).

Antibody production and cell-mediated immunity are immune responses associated with distinct patterns of cytokine production that are often reciprocal. Antibody production and cell-mediated immunity are often reciprocal immune responses associated with two patterns of cytokines originally identified in mouse CD4 T cells (*2*): T helper 1(T_H1) cells secrete interleukin-2 (IL-2), interferon γ (IFN-γ), and lymphotoxin and are associated with cell-mediated responses such as delayed type hypersensitivity (DTH); the T_H2 pattern includes IL-4 and IL-5 and is associated with antibody and allergic responses (*3*). These patterns also occur in humans (*4–7*). The T_H1 and T_H2 patterns probably represent the most extreme functional differences between CD4 T cells, but further complexity is added by the existence of other cytokine secretion patterns, such as the T_H0 pattern that includes most or all of the T_H1 and T_H2 cytokines (*8, 9*). Some or all of theses cytokines may also be secreted by other cells, which thus contribute to the patterns.

During parasitic infections there can be a dichotomy between these two immune responses. For some infections, a cell-mediated/T_H1 response provides a cure but antibody/T_H2 responses are ineffective; for other parasites the reverse is true (*10, 11*). In general terms, infections by viruses and intracellular pathogens are often better controlled by cytotoxic (T_H1 and cytotoxic T cell) responses, whereas infections by extracellular parasites and bacteria may be inhibited more effectively by antibody/T_H2 responses. Considerable cross-regulation exists between the two responses, and each can inhibit the other via their characteristic cytokines (*12*). Thus, for each infectious agent, the immune system must choose the correct response that will mediate resistance.

HIV infection may potentially be combated at two levels. Antibody may be useful for preventing initial infection by free virus, but the high levels of antibodies produced by most HIV+ patients do not eradicate an ongoing infection or prevent progression to AIDS. There are tantalizing suggestions that a cytotoxic/cell-mediated response may be more useful for dealing with established infection. T cell proliferative and cytotoxic responses to HIV peptides have been demonstrated in some individuals who have been exposed to HIV but are healthy and do not produce antibodies against HIV (*13–16*). T cell proliferation normally indicates a cell-mediated rather than an antibody response, and so these results raise the exciting possibility that a cell-mediated/cytotoxic response against HIV may be more effective than an antibody response for holding the virus in check and preventing progression to AIDS.

Clerici, Shearer, and colleagues (*17, 18*) have suggested that, during the early stages of HIV infection, there is a selective loss of immune responses against recall antigens—that is, antigens of common infectious agents to which individuals are normally immune. This is followed, they argue, by a transient bias toward T_H2-like responses in vitro, including a decreased ability to produce IFN-γ and IL-2 and enhanced ability to produce IL-4. These selective immune defects are followed by loss of additional immune functions, then a decline in CD4 cell numbers, and finally susceptibility to frequent infection by common pathogens. Because of the theoretical advantages of T_H1-like responses for defense against viruses, great interest has been generated by the suggestion that a T_H2 bias, and hence T_H1 inhibition, contributes to the loss of control of the immune system over HIV infection, resulting in progression to AIDS.

Two major features of this model have now been tested, with complex results. In this issue of *Science*, the study by Graziosi, Fauci, and collaborators directly assesses the cytokines expressed in lymph nodes of patients with HIV by measuring cytokine mRNA (*19*). Previous work by the same group has indicated that HIV is present in large amounts in lymph nodes, which may be major sites both of infection and immune responses against HIV and other pathogens (*20*). Thus, the cytokine patterns in lymph nodes of HIV+ patients should be a very significant measure of the status of the immune response. Graziosi *et al.* clearly indicate that there is increased expression of a number of cytokines in lymph nodes from HIV+ patients, but that there is not an overall shift in the cytokine patterns toward the T_H2 subset. Interestingly, most of the cytokines were made by cells other than CD4 T cells. CD8 and other cells produced IFN-γ, and non–T cells produced IL-10. In view of the importance of CD4 T cells as a source of cytokines and their role in immune responses, it is surprising that CD4 cells accounted for very little of the cytokine mRNA in lymph nodes. For some cytokines, even the low levels detected could have been contributed by minor contamination of the purified CD4 cells by other populations. Thus, the lymph node environment does not show any bias toward T_H2 cytokines, but it has not yet been possible to clearly identify the cytokines made by the CD4 population, especially the crucial subset specific for recall antigens.

The study by Maggi, Romagnani, and collaborators makes two major points (*21*). First, among large panels of T cell clones from normal and HIV+ individuals, general T cell populations do not show a bias toward T_H2-like cytokine patterns during progression to AIDS. However, the important T cell population specific for recall antigens did show a moderate shift toward the expression of T_H2 as well as T_H1 cytokines —that is, increased numbers of T_H0 clones were obtained. Thus, there is moderate support for a selective change in cytokine patterns in this population, but not for a general massive alteration to T_H2. The second point made by Maggi *et al.* is that HIV replicates preferentially in T_H2 and T_H0 rather than T_H1 clones in vitro. This provides both an explanation and a further conundrum. If the patient's immune response was pushed toward T_H2 for environmental reasons, the virus may replicate more easily and the disease would spread faster. However, selective infection and destruction of T_H0/T_H2 CD4 cells would tend to leave predominantly T_H1 cells rather than the T_H0-like cells specific for recall antigens.

Both of the studies reported in this issue of *Science* examine cytokine synthesis in

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stimulated, freshly isolated peripheral blood lymphocytes . In contrast to the earlier studies of Clerici and Shearer, no T_H2 bias was found during the progression to AIDS. Several experimental differences may have contributed to these discrepancies. In the paper by Graziosi *et al.*, short stimulation times of 4 hours were used so that the cytokines synthesized by the T cells would indicate the immediate potential of the cells. In the Clerici studies, longer stimulation periods were used, which may have allowed both activation and differentiation of the T cells. Also, both the Graziosi and Maggi studies concentrated on the period of declining CD4 cell numbers, whereas the Clerici studies identified a T_H2 cytokine bias in a particular subset of patients at an earlier stage in the disease, characterized by differential responsiveness to recall antigens and alloantigens.

There is a critical difference between the types of cells used in different aspects of these studies. Lymphocytes circulating in peripheral blood should comprise both naïve cells and memory T cells that can respond against environmental pathogens. These cells represent the potential immune responses of the individual, and their cytokine patterns have to be revealed by stimulation with recall antigens, alloantigens, or polyclonal activators such as phytohemagglutinin. Lymph nodes are major sites of immune reactions, and cytokines expressed in vivo represent the ongoing responses. The studies of Clerici and Shearer, and the results of Maggi *et al.* in this issue suggest that HIV infection causes a selective defect in T cell responses against recall antigens. Because it is defects in these recall immune responses that allow the opportunistic infections that define AIDS, it would be illuminating (but technically difficult) to analyze the cytokines expressed by antigen-specific T cells in lymph nodes during a response to recall antigens.

A model of HIV infection can accommodate much of the complex cytokine data now available. On initial entry, HIV may be neutralized by antibody, but if it escapes this mechanism, or no antibody is present, then a cell-mediated/T_H1/cytotoxic T cell response may be more useful for containing or eradicating the ensuing infection. HIV replicates preferentially in activated CD4 cells, presumably taking advantage of ongoing responses against environmental antigens. These include potentially infectious agents that are normally harmless, because immune responses effectively prevent discernable infection. HIV will thus selectively infect and kill useful T cells and progressively deplete memory responses as assessed by cytokine production of circulating T cells. In lymph nodes, HIV may preferentially replicate in activated T_H0 or T_H2 cells. This could induce generalized cytokine production by non–antigen-specific cells responding to infection and cell damage, but high levels of T_H2 cytokines may not be seen because of the death of infected T_H0/T_H2 cells. Non-activated T cells specific for other recall antigens may not be infected, so circulating T cells in blood could present a different picture than lymph nodes.

The apparently conflicting results of different studies may be explained if there is a balance between the induction of a T_H2 bias during infection, and rapid killing of T_H2 and T_H0 cells. This hypothesis could also explain why allergy and immunoglobulin E (IgE) levels, correlated with T_H2-like responses, are not dramatically elevated in HIV patients, but high IgE levels predict more rapid progression to AIDS (*21*). Coupled with the data indicating a subtle T_H2 bias and yet increased susceptibility of T_H2/T_H0 cells to infection, this could mean that HIV induces a moderate bias toward T_H0/T_H2 responses and takes advantage of such responses to replicate more effectively. This would also mean that the destruction of the immune system may proceed faster in areas where there is a high parasite infection rate, as many helminth parasites induce very strong T_H2 responses that can interfere with antiviral responses (*22*).

In future experiments, it will be important to resolve the discrepancies in the cytokine data from peripheral blood, hopefully by different laboratories using the same protocols. It is important to find out whether HIV selectively infects normal T_H0/T_H2 cells in the same way as clones. Does HIV induce a T_H0/T_H2 bias in immune responses, or does it only take advantage of such responses induced by other agents? Macrophages are also infected by HIV, and CD8 cells have the potential to kill HIV-infected cells, so it is crucial to understand the effect of HIV on the normal interplay between these cell types and CD4 T cells. In addition to the $T_H1/T_H0/T_H2$ effector CD4 T cell types, there is also a large population of precursor cells that secrete mainly IL-2, and then differentiate into one of the effector types. What is the susceptibility of these cells to infection, and does HIV influence their differentiation?

T_H1-like cells may resist direct HIV infection and also be more able to induce destruction of infected cells. The immune response against the actual HIV viral components is crucial. Patients who have cell-mediated but not antibody immunity against HIV are extremely important: Have they been infected and brought the virus under control or were they exposed to viral antigens without having been genuinely infected? It is conceivable that we could live with HIV infection provided the immune system could contain the infection, in the same way that infection by some herpes viruses can be life-long, yet cause minimal symptoms unless the immune system is suppressed. If a T_H1-like, cell-mediated, non-antibody response can control HIV, this has enormous importance for the design of vaccines and strategies for treating HIV-infected patients.

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