Conventional cytotoxic T lymphocytes (CTLs) that express the CD8 co-receptor alongside their clonally distributed receptor for antigen are superbly equipped to eliminate virus-infected cells. They recognize short peptide fragments of intracellular pathogens which are brought to the surface of the infected cell in the groove of the major histocompatibility complex (MHC)-encoded class I molecules (1). Once a resting CTL is induced to full effector function by appropriate stimulation with antigen-presenting cells, it can recognize and kill an infected target cell very efficiently. The elimination is swift, and the CTL itself can detach and attack another target cell (2). The mechanism by which the target is killed is most commonly by the insertion of perforin pores in the target membrane, allowing the entry of enzymes, called granzymes, that originate from the same granules within the CTL as does the perforin. Inside the target cell the enzymes activate a death program leading to apoptosis of the cell. For target cells that express the Fas molecule on their surface, CTLs have a second method of cytolysis, employing a Fas ligand to trigger apoptosis by this receptor–ligand interaction (3). On recognition of antigenic cells, CD8+ T cells also secrete γ-interferon, which induces a resistance to virus in neighboring cells and stimulates the activity of phagocytic cells.

In many human and animal models of acute viral infection, specific CTL effector activity is induced rapidly, and the cells travel in the blood to all the sites of infection and eliminate every infected cell (4, 5). Infection with human immunodeficiency virus type 1 (HIV-1) also shows this early acute period during which CTLs and other immune mechanisms are induced (6, 7). But the infection is not eliminated. It is followed in many cases by a latent period which evolves into a titanic struggle within the lymphoid organs during which virus is produced in large amounts in the face of an ongoing CTL response. In later stages of the disease, CD4+ T-cell counts drop, CTL effector activity wanes, and the immune system loses the battle.

Recent studies of what is going on in the central lymphoid organs of HIV-infected individuals (8, 9) and mathematical analyses of what happens in peripheral blood when the “steady state” is disturbed (10, 11) give us a glimpse of the battle. In symptomatic AIDS patients with CD4+ T-cell counts less than 500/mm3 of blood it appears that around 105 HIV virions, about one-third of the total viral load, are being produced and cleared daily. In addition, about the same number of CD4+ T cells, representing about 1% of total, are produced and destroyed daily. Decreasing the viral load to about 1% of the starting steady-state levels with drugs directed against the viral reverse transcriptase or the protease was used to reveal these dynamic figures. The antiviral treatments also revealed that drug-resistant variants emerge and reestablish the levels of viremia and the gradual CD4+ T-cell loss within a 2-week interval. This has refocused attention on the importance of the genetic variability of the pathogen, which is due to the error-prone reverse transcriptase coupled with the rate of virus replication (12). Although similar kinetic data are not available for asymptomatic HIV-infected persons, such individuals do maintain a plasma viremia, albeit 10- to 100-fold lower than in AIDS patients, and it is likely that a similar rate of virus production from newly infected cells is occurring at this stage of HIV infection.

So why can't the specific immune effectors, including CTLs, eliminate all productively infected cells? Suggestions for this have centered on the escape of the virus by epitope mutation—i.e., antigenic drift (13). This would clearly seem to be a feasible option for HIV, based on what was seen in the drug treatment studies. Another approach is to look at studies on persistent infection of mice with lymphocytic choriomeningitis virus (LCMV), which have led to the idea that the pathogen has been modified, high-level antigen exposure may exhaust the CTL response (14). The paper in this issue of the Proceedings by Moss et al. (15) confirms that HIV-infected individuals do maintain a high number of circulating CTLs specific for HIV epitopes. Up to 1% of the circulating CD8+ T cells score as HIV specific. In this study, sequence analysis of the T-cell receptor genes showed that some CTL clones may be present in the patients for long periods of time. High levels of circulating CTL effectors imply a high level of target antigen. If epitope-escape mutants are not selected by the CTL response, then this must be taken to imply that this arm of immunity is not a threat, not a selection pressure, on the infected cells that are producing most of the virus in the blood. Thus, CTLs may be constantly triggered by large amounts of antigen, but there may be a reservoir of infected cells responsible for most virus production which is somehow shielded from attack by CTLs.

The existence of high levels of CTL effector activity in infected animals, which is implied by the ability to detect killing of peptide-coated or infected targets by peripheral blood cells taken directly from the animal and which may be confirmed by molecular means, is taken as strong evidence that those T cells are seeing a lot of antigen in vivo. Without constant antigenic stimulation CTLs disappear. This is well illustrated by LCMV infection of immunocompetent mice. During the course of an acute infection with LCMV, CTLs exist at about the 1% level. When antigen is eliminated at about day 10, the numbers of CTLs decline rapidly to 1/30th their previous level and effector activity disappears altogether (16). The memory of the CTL response remains with the animal for life as an increased number of memory CTLs which can be rapidly reinduced to effector function on reexposure to the viral antigen. In this “normal” case the CTL response is well regulated. While antigen (infected cells) is around, CTLs divide and become effector cells. When antigen is cleared, most or all CTL effectors die, leaving behind a population of memory cells from each clone of CTLs in expanded numbers (16, 17).

The strain of LCMV can be selected, or the host can be modified, to give a different tempo of infection. When more aggressive strains of virus are used or the host is compromised by age, irradiation, or depletion of T cells, the infection can become chronic, with a fine balance between viral persistence and elimination by the host immune response (18, 19). With further insult to the immune system, the CD8+ CTL response may be eliminated or exhausted, and the mice will go on to become carriers. This is an interesting scenario, which may relate to HIV infection, but does not explain why a high level

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of CTL effector activity coexists for years with HIV-infected cells. If the high level of circulating CD8+ CTL activity specific for HIV epitopes is taken to mean that a lot of antigen is present, the next question is to ask whether the antigen remains constant or is a moving target. Given the high mutation rate of HIV in each host, it is obvious that it could present a moving target for the immune response. In the case of the peptide epitopes of viral proteins that are presented to CTLs there are many ways to avoid a CTL response (13): substitutions of anchor residues in the peptide would prevent binding to the MHC groove and provide the easiest route of escape from a polyclonal CTL response. Variation in peptide residues that point out of the MHC groove would allow escape from recognition by some T cells and might even antagonize (inhibit) the activity of other CTLs. Changes in such residues would, however, provide new antigenic epitopes for new classes of CTL. Evidence for all of these possibilities has been presented but in no case is it clear that CTL presentation was responsible for selecting the epitope mutation. The more common finding—that the specificity of the CTL response in HIV-infected individuals can remain constant and that the level of this activity can remain high—is taken here as evidence that CTL-mediated killing is not a dominant selection pressure on the virus.

The finding of high CD8+ CTL activity in HIV-infected individuals and the lack of evidence for CTLs as the primary selective force in HIV evolution poses a conundrum. As a solution one might suggest that the main virus-producing cells may be resistant to HIV-specific CTL-mediated lysis yet their viral product may be processed by other cells to stimulate the CTLs. Processing in this case could mean infection of a cell where proviral integration and viral protein production, followed by MHC class I presentation, occur normally. Or it could mean the uptake of virus particles, or necrotic infected cells, by professional antigen-presenting cells (macrophages and dendritic cells) in the central lymphoid organs for presentation on MHC class I molecules to CD8+ T cells. Although it is usual to think of MHC class I-associated peptides as originating not only from endogenously synthesized proteins, it is clear that professional presenting cells can present exogenous, particulate antigens in association with MHC class I molecules (20, 21). In this way, nonproducer cells can provide the antigenic stimulus for MHC class I-restricted T cells.

What is the mechanism by which productively infected cells resist CTL-mediated lysis? If these cells fail to express MHC class II molecules, they would also not serve as targets for HIV-specific CD4+ effector T cells and might as well be capable of transferring the HIV genome to susceptible cells in the face of neutralizing anti-HIV antibody by a virus-dependent fusion event. To avoid recognition and destruction by HIV-specific CTL effectors, these cells would either have to be deficient in a critical step in HIV antigen processing and presentation or have constitutively low (or downregulated) levels of MHC class I molecules. It seems unlikely that a cell type harboring HIV would be defective under normal physiological conditions in the presentation of foreign antigens to CTLs, since such a cell type would be a potential reservoir for all viruses and other intracellular parasites. It seems more likely that one or more HIV gene products may act selectively in this cell type to inhibit HIV peptide presentation and/or CTL recognition. In support of this concept, there is some evidence in human herpes simplex virus 1 (HSV-1) infection for a cell lineage-dependent inhibitory effect of a viral gene product on HSV antigen presentation to CTLs (22). It has also been reported that the HIV-encoded transactivator protein Tat can lead to repression of MHC class I gene promoter activity (23).

There are many other variations on this and related themes ranging from antagonism to disregulation of CD8+ T-cell subsets which could account for the impotence of HIV-specific CTLs in virus clearance. Perhaps it is time to entertain the possibility that the *in vitro* analysis of spontaneous or induced cytotoxic activity by HIV-specific CTLs on target cells does not represent the presence of fully differentiated activated CTL effectors with antiviral activity in HIV-infected individuals. Unlike most viruses HIV is lymphocytotropic. Infection of CD4+ T cells (or of a critical antigen-presenting cell in *vivo*) could lead to abnormal differentiation of CTL precursors into effector cells which can be triggered to lyse peptide-coated or HIV gene-expressing target cells in *vivo* but are ineffective at virus clearance in *vivo*. Perhaps rather than asking "Why can't cytotoxic T cells handle HIV?" we should be asking "Are the CD8+ T cells with cytotoxic activity detectable in HIV-infected individuals really antiviral cytotoxic T cells?"

The inability of CTLs to contain HIV raises a broader question: Do CTLs play a central role in immunity to most viruses? There is convincing evidence for CD8+ CTL- and perforin-dependent lysis as an essential effector mechanism in virus elimination during experimental LCMV infection (24, 25). In other experimental models, however, the requirement for a CD8+ CTL response to eliminate virus and promote recovery is less clear. In particular, in several models of experimental virus infection, studies on the susceptibility of mice rendered deficient in DC8+ T cells by targeted gene disruption suggest that other immune mechanisms—CD4+ T-lymphocyte effectors, neutralizing antibodies, etc.—can facilitate virus clearance and recovery (26). Likewise, in viral infections in humans, while there are convincing data for CTL-dependent virus clearance at least in chronic human cytomegalovirus infection (27), evidence for CTLs as major antiviral effectors in other human virus infections is less convincing. This is perhaps best illustrated by the type A influenza virus. Humans can mount a memory CTL response against common epitopes on several conserved components of viruses of different subtypes. Yet as the pandemics of 1957 and 1968 illustrate, the presence of type common memory CD8+ T cells in influenza immune individuals does not confer immunity to pandemic and, indeed, even to interpandemic influenza outbreaks. One might argue that in human influenza infection the failure of crossreactive CTLs to confer protective immunity reflects a waning of the memory CTL response to these conserved internal peptides within the human population in the time interval between influenza epidemics. Alternatively, since CD8+ memory T cells must activate and differentiate before becoming CTL effectors, infection with new epidemic influenza strain could be well established in the respiratory tract before crossreactive CTL precursors differentiate into active effectors. Neither of these arguments can be invoked to account for the ineffectiveness of the CTL responses to HIV.

Our perceptions about the role of cellular immunity in viral infection rest on the success of vaccination strategies using the smallpox and polio paradigms. The slow progress in understanding the pathogenesis of AIDS and the contribution of cellular and humoral immunity in HIV infection suggests that these paradigms are not adequate and that a new paradigm of antiviral immunity will need to be established in order to treat and prevent HIV infection. Whether this paradigm shift will reflect a new understanding of cellular reservoirs for virus, a redefinition of lymphocyte activation and differentiation, or an as yet unsuspected novel interaction between HIV and the immune system remains to be determined.