Position paper

A role for CD8+ T lymphocytes in the pathogenesis of AIDS

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SUMMARY

Experimental and clinical evidence is presented which supports the hypothesis that CD8+ T lymphocytes aimed at suppressing HIV replication in infected CD4+ T cells may have an important role in the pathogenesis of AIDS by directly causing a decrease in CD4+ T lymphocyte numbers. Possible models to test this hypothesis are discussed.

Key-words: AIDS, HIV, Replication, T lymphocyte, Immunosuppression; Clonal anergy, Graft *vs.*, Host disease, Experimental immunodeficiency; Position paper.

Introduction

The life cycle of a retrovirus is such that the newly infected cell must undergo at least one round of DNA replication and mitosis for the synthesis of new virus to begin (Weiss *et al.*, 1985). HIV is a retrovirus widely held to be the aetiological agent of AIDS. Several HIV-associated mechanisms have been described to explain the cytopathic effects on CD4+ T cells observed *in vitro*, but so far none of these mechanisms has been observed *in vivo* (Garry, 1989). Many HIV isolates obtained from AIDS patients are poorly cytopathic *in vitro* and non-cytopathic HIV isolates have been associated with disease (Levy, 1988). Usually, non-dividing lymphocytes cannot be productively infected by retroviruses like HIV; only the antigen or mitogen-activated ones can. Infection of unactivated T cells leads to incomplete reverse tran-scription of HIV RNA; the truncated DNA copy is extremely unstable, with a half-life of only 24 h (Zack *et al.*, 1990). Activation of HIV-infected lymphocytes also seems to be necessary to induce the replication of HIV; virus production has been observed only in lymphocyte cultures exposed to antigens, whereas no virus was produced in absence of antigenic stimulation (Fauci, 1988; Ho *et al.*, 1989; Coombs *et al.*, 1989).

It has been possible to isolate HIV from peripheral blood lymphocytes (PBL) of most HIV-seropositive patients by cocultivation with freshly activated PBL regardless of the clinical stage of infection (Ho *et al.*, 1989; Coombs *et al.*, 1989). However, plasma viraemia has been found to correlate with the clinical stage of infection, but only 45% of patients with plasma viraemia had HIV p24 antigen in either serum

or plasma, and no correlation was found between the amount of p24 antigen in plasma and the plasma HIV titres (Coombs et al., 1989). Cohort data show that over time, increasing numbers of patients with preserved high titres of p24 antibody and without detectable titres of p24 antigen develop AIDS. No explanation has been offered for these findings or for the failure to detect viral antigens in 30-50 % of patients (Cheingsong-Popov et al., 1991).

At least one other virus is currently known to have the same major target cell as HIV: the human herpesvirus-6 (HHV6). Infection with HHV6 is quite common in the general population and it is a fact that several HHV6 strains are directly cytopathic for both PBL and purified CD4$^+$ T lymphocytes (Takahashi et al., 1989; Levy et al., 1990; Carrigan et al., 1990). It has been shown that HHV6 has preferential tropism for activated cells and that addition of cytokines to infected cultures stimulates the production of HHV6 (Lusso et al., 1988; Carrigan et al., 1990); both features are shared by HIV (Fauci, 1988; Garry, 1989). Nevertheless, there are no reports of immunodeficiency induced by HHV6 in spite of the clear virus-induced cytopathic effects on CD4$^+$ T cells. This suggest that HHV6 is unable to trigger other mechanisms that may cause an immunocompromised state.

However, the finding that levels of HIV in plasma and PBL are higher than previous estimates has reinforced the idea that HIV direct cytopathic effects alone may be sufficient to explain much of the pathogenesis of AIDS (Ho et al., 1989; Coombs et al., 1989; Baltimore and Feinberg, 1989); but let us consider the case of the common cold which can be caused by a large number of viruses belonging to not less than four different groups (adeno-, rhino- coxsackie and corona viruses). Nevertheless, all such different viruses are able to cause the same clinical syndrome because all of them are cytopathic viruses that share the same main target cell population. This fact indirectly suggests that in the case of HIV and HHV6 there may be something more than just the killing of their common target cell population to explain why only HIV causes AIDS.

The key and obvious difference between HIV and HHV6 is that HIV is a retrovirus and as such, it needs host-cell activation for its own replication, while HHV6 is a herpesvirus independent of host-cell activation for its own replication. If HIV replication depends on CD4$^+$-cell activation, then suppression of HIV replication can be achieved by suppressing CD4$^+$-cell activation, while in the case of HHV6, its replication can be controlled by other mechanisms which do not target the activation of the host cell.

Viral-induced disease may be due to immunopathological processes and not to viral lysis for their development. In such cases, the incubation period is related to the time for these immunopathological events to result in disease, and not to the period of viral replication. In such situations, the strength of viral replication is not directly related to the severity of clinical illness; the incubation period depends on the mechanism by which the disease is produced, host factors and the virulence and dosage of the infecting agent (Evans, 1989).

Paradoxes in the natural history of HIV infection

The current picture of HIV infection shows that there are three phases: a short acute phase during which high levels of virus are produced, a chronic phase characterized by very low level of HIV expression, and a crisis, terminal phase where a recrudescence of viral replication occurs (Baltimore and Feinberg, 1989; Clark et al.,

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AZT   = azidothymidine.
GVHD = graft-versus-host disease.
MAIDS = murine acquired immunodeficiency syndrome.
MuLV = murine leukaemia virus.

PBL   = peripheral blood lymphocyte.
SIV   = simian immunodeficiency virus.
SSCA = spontaneous suppressor cell activity.

1991). It is important to stress that the early acute phase is clinically characterized by a mild flu-like or mononucleosis-like syndrome. The time from infection with HIV to onset of the acute clinical illness is generally 2-4 weeks. The clinical illness usually lasts for 1 to 2 weeks and most of the symptoms are self-limited and do not recur after resolution (unlike symptoms associated with EBV mononucleosis). Following HIV infection, there is an intense period of viral replication demonstrated by the ease of viral isolation and high levels of plasma HIV p24 antigen. The frequency with which HIV can be isolated decreases following seroconversion, and plasma levels of HIV p24 decrease to undetectable levels. Antibodies that inhibit synctium formation *in vitro* and antibodies that mediate antibody-dependent cellular cytotoxicity against virally infected cells develop soon after seroconversion. These findings suggest that the immunological response to primary HIV infection is favourable in the short term (Tindall and Cooper, 1991; Clark *et al.*, 1991).

However, a CD8+ lymphocytosis with atypical lymphocytes has been observed in primary HIV infection in the second week after the onset of illness (Tindall and Cooper, 1991). A similar CD8+ lymphocytosis is characteristic of primary cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infection. In EBV infection, the CD8+ cells have been shown to control infection by killing virus-infected B lymphocyte or suppressing virus replication (Svedmyr and Jondal, 1975). The increase in CD8+ cell numbers during primary HIV infection occurs concomitant with resolution of clinical symptoms and a sharp reduction in the amount of plasma HIV p24 antigen (Cooper *et al.*, 1988). It has been reported that during the first weeks of primary HIV infection, there is a decrease in the responsiveness of lymphocytes to antigens and mitogens (Cooper *et al.*, 1988); a significant decrease in circulating CD4+ cells at the time of Western blot seroconversion, has also been observed; such a reduction in CD4+ cell numbers was not present during the preceding period when the Western blot was negative. However, prior to Western blot seroconversion, there is an increase in CD8+ cells (Wolinsky *et al.*, 1989).

Azidothymidine (AZT), an inhibitor of viral reverse transcriptase, can produce a significant reduction (up to 25-fold) in HIV plasma titres when compared with the mean plasma titres of untreated patients with AIDS or AIDS-related complex (Ho *et al.*, 1989). However, in spite of its clear effect upon HIV replication, AZT produces only a very transient increase in CD4+ cell numbers. It is true that the levels of CD4+ T cells correlate with disease progression, but it is likely that by the time such levels decline, the damage to the host's immune system is probably irreversible (Baltimore and Feinberg, 1989). A profound CD4+ lymphocytopenia is not solely characteristic of HIV infection; severe CD4+ cell depletion may occur in patients with visceral leishmaniasis or *Pneumocystis carinii* pneumonia in the absence of HIV infection (Cozon *et al.*, 1990; Gautier *et al.*, 1991). It is certain that the HIV titres produced during the chronic phase of infection are so low that they can be excluded as the cause of a meaningful reduction in CD4+ cell numbers.

The proportion of CD4+ T cells infected with HIV in asymptomatic subjects is low (1 in 2,500 to 1 in 26,000). Although high proportions of the infected cells contain replication-competent provirus copies, this is fully compatible with good health and a high number of CD4+ T cells in the blood even after 4 years of infection with HIV (Brinchmann *et al.*, 1991). Lymph nodes have been shown to contain an average of only 0,001 or fewer HIV DNA copies per cell, and there is no evidence of sequestration and destruction of large numbers of HIV-infected CD4+ T cells in lymph nodes (Shibata *et al.*, 1989). An important question is whether HIV-infected bone marrow CD34+ stem-progenitor cells serve as a significant reservoir of virus in HIV-infected individuals. However, it has now been shown that infection of bone marrow stem/progenitor cells with HIV occurs rarely, if ever, *in vivo*. Thus, infected stem cells are not a major source of persistent HIV and do not account for haematopoietic suppression (Davis *et al.*, 1991). It is difficult to accept that a cytopathic effect by HIV on individual infected cells can kill a sufficient num-

ber of CD4$^+$ T cells to exceed the capacity of generation of new CD4$^+$ cells if this remains normal (Ludyard and Grossi, 1989). Recent reports about the virus load in CD4$^+$ T cells from asymptomatic individuals suggest that few of this cells are likely to be lost as a direct consequence of infection by HIV and that additional mechanisms may contribute to the depletion of CD4$^+$ cells (Brinchmann et al., 1991).

Role of CD8$^+$ suppressor cells in the pathogenesis of AIDS

So far, potential treatments for AIDS have been designed with the intention of inhibiting or suppressing HIV replication. However, current evidence suggests that when HIV replicates actively, it produces only a mild mononucleosis-like syndrome (Steeper et al., 1988; Tindall and Cooper, 1991). Thus, perhaps the immune reaction triggered by the CD4$^+$ T-cell activation necessary to permit further HIV replication is the cause that finally leads to immunodeficiency and major pathology.

For some time, it has been realized that suppressor T cells can be a suitable mechanism for limiting immune responses to a foreign agent when the foreign agent is not quickly elimitated, as in chronic infections or parasitic infections, and various types of established organ transplants (Nossal, 1989). For example, self-reactive T cells that mature in the thymus and enter the periphery could be functionally inhibited by other T cells (suppression/immunoregulation) when these self-reactive T cells encounter the antigen they recognize, thus leading to clonal anergy. It has been shown that clonal anergy can account for antigen-specific tolerance induced in mice (Rammensee et al., 1989). It has also been shown that CD8$^+$ suppressor T cells can induce clonal anergy in CD4$^+$ T cells responding to Mycobacterium leprae antigens in vitro, a fact which suggests that suppressor T cells may operate by interfering with the delivery of co-stimulatory signals to other antigen-stimulated T cells (Mueller, 1989).

It has been found that CD8$^+$ T cells from HIV-infected subjects, but not from seronega-

tive controls, are able to suppress the replication of HIV in acutely infected CD4$^+$ T cells in vitro, but also in PBL from HIV-infected individuals. This suppression was partly mediated by a diffusible factor, but not by a direct elimination of cells by cytotoxic cell activity; instead, virus production was suppressed. It is noteworthy that complete suppression of virus replication was achieved in vitro even with low numbers of CD8$^+$ T cells from HIV-infected individuals (Walker et al., 1986; Walker and Levy, 1988; Walker et al., 1989); this suggests that there is a tendency toward an excess of CD8$^+$ T cells not necessary for efficient HIV suppression. In some cases, T-cell defects observed in AIDS patients lymphocytes can be eliminated by purification of cells before testing for proliferation and T helper functions, suggesting that such a restoration of function might be due to the removal of suppressor T cells (Margolick et al., 1985).

The hypergammaglobulinaemia seen in many AIDS patients goes against the idea that AIDS is directly related to CD4$^+$ T-cell death, because one would expect a decrease in antibody production with decrease numbers and functions of CD4$^+$ helper T cells. It has been shown that spontaneous immunoglobulin production in vitro is inversely correlated with the percentage of CD4$^+$ T cells and is directly correlated with the percentage of CD8$^+$ T cells in PBL (Mizuma et al., 1988). It has also been observed that a drop in the number of CD4$^+$ T cells occurs only after seroconversion, since it has not been observed in HIV-infected seronegative subjects. Nevertheless, lower CD4$^+$/CD8$^+$ ratios have been observed before seroconversion; however, these are not caused by abnormally low numbers of CD4$^+$ cells, but rather by elevated numbers of CD8$^+$ cells (Imagawa et al., 1989).

Immunological abnormalities have been observed in HIV-infected homosexual men long before there is a depletion in CD4$^+$ T cells (Marion et al., 1989; Miedma et al., 1989). Cohort studies of the relationship between CD8$^+$ T-cell counts and progression to AIDS have shown that, contrary to expectations, progression to AIDS is more frequent in those HIV-

infected individuals with high early CD8$^+$ T-cell counts (Anderson *et al.*, 1991). The presence of spontaneous suppressor cell activity (SSCA) in patients with AIDS and ARC has been found; such cell populations appear to interact in producing normal or augmented downregulation of residual T-lymphocyte function, even in the face of helper/inducer CD4$^+$ T-cell depletion (Katner *et al.*, 1987). Higher levels of SSCA have been found in patients with early clinical AIDS and advanced terminal disease. Patients surviving clinical AIDS for more than one year had lower levels of SSCA compared to controls, SSCA seems to predict disease progression, since patients with ARC who showed rises in SSCA progressed to AIDS, while those with blunted SSCA did not progress to full disease (Mullin and Mayer, 1991).

The inhibitory activity of HIV replication by CD8$^+$ T cells seems to be mediated by mechanisms other than classical virus-specific MHC class-1-restricted cytotoxicity (Brinchmann *et al.*, 1990). In mice, it has been possible to isolate and characterize CD8$^+$ suppressor T-cell clones capable of inhibiting the antigen-induced proliferative responses of CD4$^+$ helper T cells clones, without detectable cytotoxicity for either antigen-presenting cells or responding cells. Such inhibitory activity is neither antigen-specific nor MHC-restricted (Hisatsune *et al.*, 1990).

Thus, the final recrudescence of HIV replication observed in terminal AIDS could only represent the final exhaustion of the host's immune system due to a CD8$^+$ T-cell-mediated chronic oversuppression which ends by down-regulating even CD8$^+$ T-cell activation. Further evidence which suggests that CD8$^+$ suppressor T cells participate in the immunopathogenesis of AIDS has been discussed elsewhere (Laurence *et al.*, 1983; Mullin *et al.*, 1987; Aranda-Anzaldo, 1990; Mullin and Mayer, 1991). Thus, while normal clonal anergy mediated by non-cytotoxic suppressor T cells is an antigen- and cell-specific process, in the case of AIDS we could be facing a suppressor T-cell mediated non-specific pan-anergy which may affect all sorts of CD4$^+$ T-cell populations.

Possible mechanisms for CD4$^+$ T-cell suppression

Comparing the proliferative responses from AIDS patient lymphocytes with the responses of lymphocytes from HIV-seronegative homosexual controls, it was found that the decreased proliferative response of AIDS lymphocytes cannot be primarily due to a deficient signal via the cell membrane receptors, since direct stimulation of the following intracellular stimulatory pathways did not normalize the response. Furthermore, it was found that AIDS lymphocytes have no major defect in interleukin-2 receptor expression and that such lymphocytes are able to produce interleukin-2 when stimulated directly via the intracellular stimulatory pathways (Hofmann *et al.*, 1989). Thus, the decreased production of IL2 seen in AIDS lymphocytes must be explained by a defect more central than the inactivation of membrane-dependent stimulatory pathways. It has already been proposed that the decreased proliferative response observed in CD4$^+$ lymphocytes from HIV-infected individuals is linked to the inhibition of the major steps leading to DNA synthesis and cell proliferation (Hofmann *et al.*, 1989; Aranda-Anzaldo, 1990).

Studies from several laboratories show that PBL from AIDS patients inhibit *in vitro* T helper responses of PBL from non-infected individuals. Soluble factors that inhibit normal T helper function have been detected in cultures of PBL from HIV-positive patients. Both the inhibitory cells and the suppressive factors blocked self-restricted T helper responses without affecting the allogeneic restricted components of the mixed lymphocyte reaction or responses to T-cell mitogens (Laurence and Mayer, 1984; Hofmann *et al.*, 1986). This suggest that selective loss of self-restricted T helper function is due to some soluble factor (or factors) produced by a subset of PBL (Aranda-Anzaldo, 1990; Shearer and Clerici, 1991).

In AIDS patients, there are thymus histological changes that suggest premature involution and inflammatory changes similar to those seen in graft *vs.* host disease (GVHD). Immune abnormalities of early HIV infection parallel those seen in what is called immunostimulatory GVH

reaction observed in mice, which leads to activation of suppressor cells that specifically inhibit the murine T helper cells (Shearer et al., 1986). It has been shown that the major effect of GVHD-induced suppressors in mice is inhibition of DNA synthesis, because such suppressors block the proliferation induced by receptor-mediated stimulation or exogenously added growth factors and do not significantly inhibit either lymphokine secretion or lymphokine receptor expression (Wall et al., 1989). These observations bear a striking similarity to those made in PBL from full-blown AIDS patients in which the proliferative response of both CD4$^+$ and CD8$^+$ T cells is defective; such a response may be increased by addition of IL2 but only to subnormal levels (Hofmann et al., 1989). Also, it is remarkable that in T-cell-induced clonal anergy observed in mice, the unresponsive T cells show a normal density of membrane T-cell receptors as well as the ability to the express IL2 receptor that parallels the situation found in GVHD and in AIDS lymphocytes. The unresponsive T cells in clonal anergy fail to proliferate because they cannot produce IL2, like the AIDS lymphocytes, which can only produce IL2 after direct stimulation of the intracellular pathways (Hofmann et al., 1989). It has been reported that fulminant viral disease induced by molecularly cloned strains of simian immunodeficiency virus (SIV), in affected monkeys produces pathological changes in the gastrointestinal tract typical of an immunologically mediated reaction like GVHD (Martin, 1990).

Thus, in an antigen-stimulated host, there will be a persistently activated helper T-lymphocyte population subject to downregulation by an active suppressor T-cell population. The introduction of HIV into this system generates a new population of activated T cells that need to be suppressed to avoid replication and spread of HIV. Suppressor T cells will produce soluble factors able to stop HIV replication by inhibiting DNA replication in the host cell or by blocking the entry of HIV-infected cells into the S phase of the cell cycle. These two mechanisms are not mutually exclusive. The suppressor soluble factors will be able to block DNA replication not only in HIV-infected cells but also in non-

infected CD4$^+$ lymphocytes. HIV replication might be contained and controlled for some time by a combination of antibody-mediated mechanisms and CD8$^+$ cell-mediated suppression. This will produce a population of latently (or persistently) HIV-infected CD4$^+$ lymphocytes susceptible to be clonally or polyclonally activated through the years by whichever new antigenic stimuli the host shall be exposed to. This will lead to a new cycle of helper T-lymphocyte suppression mediated by CD8$^+$ cells, thus generating a vicious cycle of activation-suppression-activation, etc. in which factors with a blocking effect on CD4$^+$ T-cell replication will have a critical role.

The loss of the equilibrium between activation and suppression will be favoured in high-risk groups exposed to continuous antigenic stimulation, leading to a state of immune over-suppression in which certain CD8$^+$ T-cell subsets less susceptible to downregulation by the normal homeostatic controls of the immune network will take a leading role. As a consequence of this, the CD4$^+$ cells will be the first lymphocyte population to decline with a consequent decrease in the production of lymphokines necessary for the activation of macrophages and the maturation to effector function of natural and other constitutive killer cells. Finally, even the CD8$^+$ T-cell numbers will decline due to a lack of the appropriate helper T-lymphocyte stimulation. Nevertheless, the relative number of CD8$^+$ cells will remain elevated in the immunodepressed subjects.

Models for testing the present hypothesis

There exist several models of virus-induced immunodeficiency in mice, cats, cattle and monkeys (Weiss, 1989). Although none of the clinical syndromes observed in these animal models is completely equivalent to human AIDS, such animal models remain the only possible source of in vivo experimental data. Animal models are suitable for testing the suggested hypothesis that reduction or elimination of CD8$^+$ suppressor T cells may lead to clinical improvement or abrogation of the immunodeficient state.

For example, severe experimental immunodeficiency can be induced in mice by a murine leukaemia virus (MuLV), which is replication-defective. Although in this model, there is no evidence that the virus infects murine helper T cells, the B-cell hyperplasia, hyperglobulinaemia and immunosuppression observed seem to be dependent essentially on the presence of T lymphocytes, since the defective virus affects nude mice much less severely (Aziz *et al.*, 1989).

Current evidence shows that there is an extremely low level of HIV provirus present in the circulating PBL from HIV-infected persons, and that more than 99 % of the lymphocytes which contain provirus do not express the virus (HO *et al.*, 1989; Schnittman *et al.*, 1989; Simmonds *et al.*, 1990; Brinchmann *et al.*, 1991). Thus, we may be facing a situation in which the observed final increase in the percentage of infected CD4+ cells in AIDS patients is a consequence of clonal growth and not of virus replication and spread. It has been shown that viral replication *per se* is not necessary to induce the murine acquired immunodeficiency syndrome, because strictly helper-free defective MuLV is able to produce such a syndrome without any evidence of viral replication (Huang *et al.*, 1989). A striking observation is that the number of infected cells is at least 1000-fold higher in diseased mice than in the newly infected ones. It was concluded that the expansion of the infected cell population occurs from cell division and not from reinfection, since these mice were found to harbour no virus able to replicate on mouse cells. The data indicate that the expanded cell population is clonal or oligoclonal, and as such, it originated from a single (or a few) infected cells which transformed or gained a growth advantage after infection by the defective retrovirus. Thus, it was suggested that interaction of such virus-modified cells with other cells of the immune system could trigger the immunodeficiency (Huang *et al.*, 1989).

There have been attempts to use some immunosuppressive drugs like cyclosporin in the treatment of AIDS, and partial beneficial effects have been observed (Andrieu *et al.*, 1988). It is known that precursors of CD8+ T cells are readily inactivated by agents that destroy or block rapidly dividing cells (such as cyclophosphamide and cyclosporin). Mature CD8+ T cells are resistant to these agents. The so-called Ts-1 cells able to produce suppressor soluble factors in response to antigens are particularly short-lived. Hence, in systems where antibody production and cell-mediated immunity are strongly suppressed because the antigen elicits more CD8+ than CD4+ T cells, elimination of the blockage induced by Ts-1 cells (either by low doses of cyclosporin or cyclophosphamide) at about the time the antigen is administered can result in enhancement of the immune response, but if the agent is given after the antigen has elicited enough CD8+ T cells, then no permanent enhancement will result (Davis *et al.*, 1980).

Thus, it is especially noteworthy that the murine acquired immunodeficiency syndrome (MAIDS) associated with proliferation of target cells that have been infected by a replication-defective strain of MuLV can be prevented, and normal T-cell function can be restored as well in these mice by treatment with cyclophosphamide, but not with other antineoplastic drugs like 5-aza-deoxycytidine or arabinosylcytosine, provided that cyclophosphamide is administered from the early days after the inoculation of mice with defective MuLV (Simard and Jolicœur, 1991). Such a paradoxical effect of an otherwise immunosuppressive drug may be explained, at least in part, by the fact that low doses of cyclophosphamide are known to preferentially eliminate the suppressor T cells from the lymphocyte population (Shand, 1979).

Conclusion

It is well know that it is possible to isolate different HIV strains, each of them having different biological properties, from the same HIV-infected person (Saag *et al.*, 1988; Chiodi *et al.*, 1989). Perhaps some strains (quasi-species) of viruses like MuLV or HIV are either replication-deficient or replication-defective such that they able to trigger and perpetuate an am-

biguous immune response in which suppressor T cells aimed at curtailing the expansion of the infected cell population have a dominant role (Meyerhans et al., 1989). It is likely that suppressor factors produced by the suppressor cells will be able to stop HIV replication by inhibiting DNA replication in the host cell or by blocking the entry of the HIV-infected cell into the S phase of the cell cycle. However, it is also possible that such suppressor factors would not be able to distinguish between cells that are latently infected, cells that actively express the virus and cells that are expanding in numbers due to the growth advantage conferred by a replication-defective quasispecies of the virus in question. The net result would be downregulation and inhibition of the whole range of the target cell population independently of infection status. It may be speculated that fully replication-competent strains of HIV would produce a balanced immune response like the one seen in classical viral infections in which cell-mediated immunity is able to restrict the spread of both the virus and the infected-cell population without causing further harm to the host.

Un rôle pour les lymphocytes T CD8^{+} dans la pathogenèse du SIDA

Des preuves cliniques et expérimentales sont avancées pour corroborer l'hypothèse que les lymphocytes T CD8^{+} visant à la suppression de la réplication du VIH dans les cellules T CD4^{+} pourraient jouer un rôle important dans la pathogenèse du SIDA en provoquant directement une diminution du nombre des lymphocytes T CD4^{+}. Des modèles en vue de tester cette hypothèse sont discutés.

Mots-clés: SIDA, HIV, Réplication, Lymphocyte T, Immunosuppression; Anergie clonale, Maladie du greffon contre l'hôte, Immunodéficience expérimentale; Mise au point.

Note added in proof:

Since submission of this article, it has been reported that cyclosporine A protects mice from the immunodeficiency disease induced by replication-defective MuLV (Cerny et al. (1991), Eur. J. Immunol. 21, 1747-1750).

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