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# HIV TARGET CELLS: EFFECT OF THEIR INFECTION BY HIV ON THE PATHOGENESIS OF AIDS

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*ABSTRACT*

*Pathogenesis of HIV infection and expression of retroviral proteins are gradually being elucidated. Antibody to HIV is a marker of past or present viral infection. The virus can be isolated from cultured lymphocytes of seropositive but not seronegative patients. Sero-epidemiological studies show that the majority of infected patients are asymptomatic carriers without biological sign of immune depression. Some then show immune abnormalities such as a decrease of CD4 cells in the blood; some patients present with lymphadenopathies or signs of AIDS-related complexes. Frank AIDS is a late stage of the disease.*

*Some cofactors increase the immunodeficiency and then accelerate the passage from asymptomatic carrier to persistent generalized lymphadenopathies or AIDS by spreading the virus into target cells, susceptible T4 cells, bone marrow precursors, or brain. These AIDS patients then present with opportunistic infections and/or malignancies like Kaposi's sarcoma, lymphoma, and/or brain diseases (dementia or encephalitis).*

The preferential tropism and cytopathogenicity of HIV for CD4 cells is now well-recognized, but the CD4 lymphocyte is not the only target cell for HIV *(Table 1)*. Other human target cells include EBV-transformed B-lymphocytes and macrophages. Indeed, the macrophage, not the CD4 cell, may be the initial target for HIV. HIV is a member of the family of lentiviruses, which are known to target the macrophage first. For example, visna virus in sheep and equine infectious anemia virus initially strike the monocytic macrophages.

In regard to the asymptomatic carrier, for some strains of HIV (e.g., HIV-1), the first target may be the macrophage. In such a situation, the patient may develop HIV-associated disease rather than the immune deficiency associated with AIDS and opportunistic infection or Kaposi's sarcoma. In fact, when the latter develops, it may signify that the CD4 lymphocyte or the bone marrow precursor cell has now been attacked by the virus. Other human target cells for HIV besides EBV transformed B-lymphocyte and macrophages include bone marrow precursor cells, and their infection may explain the defect in immune defense. Follicular dendritic cells and Langerhans cells can also be HIV targets. These different human cell types are targets for both group HIV-1 as well as the HIV-2 family.

What is the possible role of HIV infection of the bone marrow precursor cell? It has been shown by several groups that T-cell precursors from peripheral blood and bone marrow of HIV-infected patients display abnormal proliferation and differentiation. A positive correlation has also been reported between low plat-

**Table 1.**
**Target Cells for HIV-1 and HIV-2**

| |
|---|
| T4 lymphocytes including T lymphoblastoid cell lines |
| HTLV1 immortalized lymphocytes |
| EBV transformed B lymphocytes |
| Macrophages including $CD4^-$ microglial cells in brain |
| Bone marrow precursors |
| Follicular dendritic cells |
| Hela cells transfected with T4 gene |

ing efficiency of peripheral blood lymphocyte T cell-forming colonies of patients with lymphadenopathy syndrome and the probability of development of full-blown AIDS. Based on these findings, we studied the effect of HIV infection of bone marrow cells *in vitro*. In previous experiments, we used mainly a prototype HIV-1 strain. In this experiment, we obtained bone marrow from an HIV-negative donor, separated bone marrow mononuclear cells on Ficoll gradient, and in order to eliminate $CD4^+$ and $CD8^+$ lymphocytes present among bone marrow mononuclear cells, we depleted these cells using specific monoclonal antibodies to CD3, CD11, and also the CD4 molecules and then infected remaining cells with HIV and placed them into culture. Serially, at different time periods after infection, we examined virus production by measuring reverse transcriptase activity in cell-free supernatant, sequentially phenotyped the cultured cells, and observed T-cell colony formation using the methylcellulose method. The results indicated that bone marrow mononuclear cells depleted T3, T11, or both T3 and T11 were producing virus on day 15. At the same time, phenotyping showed that the infected culture failed to express T4 antigen, confirming that no T4 cells were present. Indeed, on day 8 even before virus production, T4 cells were absent. Moreover, the non-infected culture on day 15 did not express the T6 phenotype of immature T-cells. Thus, our cultured cells were differentiating *in vitro*, which is quite normal. The infected cells, on the other hand, expressed the T6 phenotype in culture signifying the presence of immature T-cells. In regard to colony formation using the methylcellulose method, there was a decreased colony formation in the infected compared to the non-infected culture. But in the three cases, T11-depleted, T3-depleted, or T4-depleted bone marrow cells, parallel findings in culture indicated that inhibition of colony formation was time-dependent. Furthermore, the same phenomenon was seen in relation to the colony phenotype: infected cells, in contrast to non-infected cells, expressed the T6 phenotype. We conclude from this experiment that HIV can infect bone marrow precursor cells and may provoke their abnormal differentiation after infection. This *in vitro* experiment corresponds closely with what has been observed in infected patients *in vivo*. Thus, infection of bone marrow T-cells may explain the immune deficiency as well as the non-reversibility of the immune deficiency syndrome.

I will next focus on a new viral isolate which may have a different tropism from others. As I mentioned earlier, the first target for HIV may be the macrophage. Recently, our laboratory obtained an isolate, antigenically speaking, an HIV-1 isolate, from a patient with acute and regressive encephalopathy but without immune deficiency. This virus was isolated only from cerebrospinal fluid (CSF), not from peripheral blood T-lymphocytes, and only when the patient had symptoms. When the symptoms disappeared, it was impossible to isolate the virus from CSF. Further, we noted that

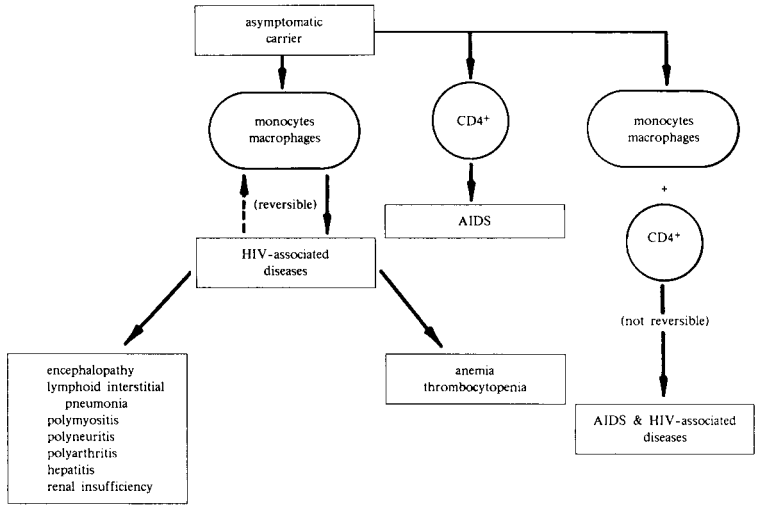


*Fig. 1. Role of HIV in the pathogenesis of HIV-associated diseases and AIDS.*

this virus could not be propagated in peripheral blood lymphocytes nor in continuous cell lines such as CEM or H9, but grew well in cord blood lymphocytes and in bone marrow cells. We wondered, therefore, whether the virus had a selective tropism for cells present in cerebrospinal fluid but absent from peripheral blood. Interestingly, this patient's disease was reversible, and he is now asymptomatic without evidence of immune deficiency. Perhaps this successful spontaneous clinical recovery concomitant with disappearance of HIV corresponds to a defense mechanism capable of controlling acute expression of the virus.

In our scheme of the role of HIV in the pathogenesis of disease *(Fig. 1)*, the asymptomatic carrier infected with HIV (either HIV-1 or HIV-2) can have virus either in monocytic macrophages or CD4 lymphocytes or both. When the asymptomatic carrier has the virus only in monocyte macrophages, what we call HIV-associated disease develops. Indeed, the findings related to our viral isolate from a patient with reversible symptoms suggests that if virus is present only in macrophages, the disease is reversible and the infection can be eliminated. But, if the asymptomatic carrier develops virus in the CD4 lymphocyte, and if the virus has passed from macrophage to CD4 lymphocyte and then spreads in the bone marrow, it may be too late. The patient will develop AIDS and, at times, AIDS in addition to other HIV-associated disease.

There remain many questions, however, without answers today. First, why does the virus spread in an asymptomatic carrier? Activation of lymphocytes has been mentioned as a way to spread the virus but it is still unclear what activates the lymphocyte, and a variety of cofactors have been suggested as activators. Further, why does the virus spread at one time in one asymptomatic carrier and at a different time in another asymptomatic carrier? Why do some patients develop tumors such as lymphomas or Kaposi's sarcoma and others develop opportunistic infection? Is it due to HIV activation of cellular or viral protein? Does HIV have an important transactivating gene? Does integration of HIV into a cell activate some cellular gene, and could lymphokine production underlie proliferation of cells? HIV might also activate a viral gene or these viruses may increase proliferation of some cells. For example, it is known that CMV, which has been implicated as a possible cause of Kaposi's sarcoma, can be activated by

HIV or perhaps the causative virus is closely related to CMV but not CMV itself. Kaposi's sarcoma and other tumors may be due to the elimination of a specific subpopulation of T4 cells. Indeed, it is not clear whether all T4 cells are infected by the virus but it does appear that only a small percentage of them can replicate the virus, and this subpopulation may also play an important role in control of tumorigenesis. In addition, more work needs to be done on the role of HIV in differentiation of cells and particularly blood cells. Finally, the relationship of activation of HIV or an HIV-gene to the expression of some oncogene should be explored as a possible explanation for special proliferation of cells in some patients. Answers to these and other questions will be important to future understanding of the role of HIV in development of various disease manifestations.

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