Mechanism for the T4 lymphopenia of AIDS

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ABSTRACT I suggest that the T4 lymphopenia of AIDS may be caused by antibodies raised against the human immunodeficiency virus that block the generation of T4 cells.

The human immunodeficiency virus (HIV), thanks to its high affinity for the CD4 receptor, infects and ultimately kills T4 cells. Thus, it is quite natural to attribute the slowly developing T4 lymphopenia of AIDS patients to this selective depleting action of HIV. But things may not be so simple.

An Old Puzzle

Explaining the impressive T4 lymphopenia occurring in AIDS solely in terms of the direct killing of T4 cells by HIV raises a serious problem: the number of T4 cells infected by HIV is negligible with respect to the greater number of "missing" T4 cells. This puzzling phenomenon has caused several researchers to ask what other cofactor may be present in AIDS.

A New Puzzle

There also is, in my opinion, another major, but rather unnoticed, puzzle: in seropositive individuals, the number of T4 cells decreases essentially linearly—that is, roughly the same number of T4 cells disappear every year (see Fig. 1). This fact strongly contradicts the assumption that AIDS' T4 lymphopenia is caused solely by HIV's direct killing of T4 cells. In this case, in fact, the decline of T4 cells would be exponential rather than linear. (With the progress of the infection, the number of HIV particles increases; thus, the number of killed T4 cells per year should also increase, except possibly at the very end, when there would not be enough T4 cells left.)* The linearity of T-cell decline also vouches against theories in which T cells are tricked by HIV into killing each other. In fact, this theory would entail that the loss of T4 cells should not be constant but instead should be highest at the beginning of the seropositive stage and smallest at the end. (For example, assume two large armies, equally armed, clash in battle. The dead will be more numerous at the early stages, when there are more troops trying to kill each other, than, say, in the middle, when only half of the troops are left alive.)

The New Theory

I put forward a simple model, the "CD4-like theory," that solves both puzzles and clarifies other phenomena as well. As it does with all foreign organisms, our body must react to HIV by producing antibodies to all of its immunogenic determinants. One of these determinants is known to be a binding site for CD4. Thus, I hypothesize that some of the antibodies raised against HIV must have a binding specificity very close to that of CD4. Let's call CD4-like such an antibody or group of antibodies. Like the copy of a key, CD4-like may be vastly

different from CD4, but will essentially have its functional value. The continual presence of the virus will then elicit the continual production of CD4-like. I now suggest that the continual presence of CD4-like may inhibit the production of T4 cells by means of either of two different mechanisms.

A Thymic Mechanism. In an adult, after an adequate T-cell repertoire has been generated, the thymus becomes less important, but it (or some thymic equivalent) may still be crucial for replacing naturally dying T4 cells, and CD4-like may inhibit their maturation. In fact, it is known (2) that precursor T cells must interact with thymic major histocompatibility complex (MHC) II cells in order to mature. If CD4 binding sites for gp120 and MHC II molecules are sufficiently overlapping [both positive (3) and negative (4) evidence for the overlapping of these two binding sites has been found], CD4-like will compete with the CD4 receptors of maturing T4 cells for this interaction. Since thymic selection is very strict, even a moderate amount of CD4-like may result in stopping the generation of T4 cells.

A Regulatory Mechanism. CD4-like may also block the generation of T4 cells by misleading a regulatory mechanism. It is possible that, in humans, the level of T4 cells is controlled by the total amount of CD4 present in the organism, whether or not on the cell surface; that is, once too many CD4 proteins are detected, T4-cell production is inhibited. (After all, cell recognition occurs via surface receptors, and a lymphocyte carrying CD4 on its surface may be an operatively adequate description of a T4 cell.) In a healthy individual, the total number of CD4 molecules is usually well correlated to the total amount of T4 cells. Thus, by regulating the amount of CD4, the organism is essentially regulating T4-cell level. But in an HIV-infected individual, even with a pronounced T4-cell lymphopenia, CD4-like antibodies may cause a "high CD4 count," misleading the organism into believing that high numbers of T4 cells are present, and thus into stopping their production. [In a species in which (the equivalent of) T4 cells are not regulated via the total amount of (the equivalent of) CD4 proteins, CD4-like antibodies should not affect the production of T4 cells in this way; indeed, it is possible that such a species may not suffer at all from (the equivalent of) AIDS.]

Solving the First Puzzle

According to the CD4-like theory, HIV does not need to directly kill lots of T4 cells to cause the impressive T4 lymphopenia of AIDS. (In principle, it might not need to directly kill a single T4 cell!) It would be sufficient for it to be "visible" for a long time to the immune system so as to elicit for a long time the production of CD4-like and thus interfere with the production of T4 cells. These cells have a finite life-

Abbreviations: HIV, human immunodeficiency virus; MHC, major histocompatibility complex.
*One may object that the observed linearity is just the net effect of two forces: the killing of T4 cells by HIV and the generation of them by the organism. This, however, would make the first puzzle even more mysterious. In fact, if the organism effectively replaces HIV-killed T4 cells, HIV should kill even more of them to produce the same T4 lymphopenia. Thus, if the number of infected T4 cells already appeared too small, it would now appear even smaller.

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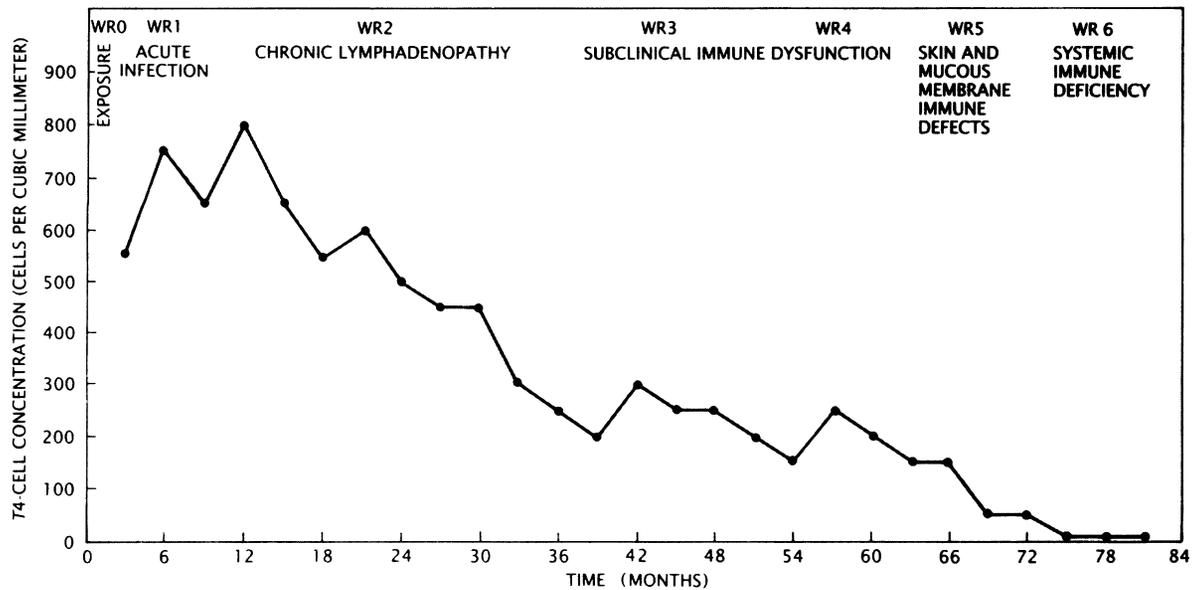*Proc. Natl. Acad. Sci. USA 90 (1993)*   10983

FIG. 1. Decline in T4-cell count (rounded to the nearest 50) was tracked in the blood of a young man whose disease followed a typical course. About three months after sexual exposure to HIV the patient tested positive for the virus; his T4-cell count dropped and then rebounded. He developed chronic lymphadenopathy at nine months and, at 51 months, after a long, slow decline in his T4-cell count, exhibited chronic, subtle abnormalities of delayed hypersensitivity. He displayed persistent anergy at 63 months but had no overt symptoms of infection until about 68 months, when he developed thrush and oral hairy leukoplakia. Less than a year later he was besieged by opportunistic infections, including cytomegalovirus infection, which made him blind. He died at 83 months. [Figure and legend reproduced from ref. 1 with permission (copyright Scientific American, Inc.).]

time and must be replaced; tampering with their replacement may be HIV's most insidious action. If, for a few years, T4 cells die of "old age" without being replaced, this will easily cause the typical T4 lymphopenia of AIDS patients.

Solving the Second Puzzle

The CD4-like theory correctly predicts that the number of T4 cells should decrease roughly linearly. This can be argued as follows. Assume that the expected lifetime of a T4 cell is, say, 7 years. Then, we expect that in the first year, essentially all (and essentially only) the cells that at the time of seroconversion were 6 years old will die; in the second year, the cells that were 5 years old will die; and so on. Since these cells will not be replaced (if in an infected adult the ages of T4 cells are distributed in a reasonably uniform manner), then roughly the same number of cells will "disappear" every year, which is exactly what is observed.[†]

The CD4-like theory is easily reconcilable with the fact that the body produces a vigorous response to HIV, as it is exactly this powerful response that causes T4-cell loss. It is also in agreement with the remark (6) that T4 depletion occurs only

after antibody formation against HIV, though the presence of antigen can be documented prior to seroconversion.

Related Theories

The hypothesized structural similarity between MHC II molecules and glycoprotein gp120 is also the basis of other theories.

Martinez-A, de la Hera, Alonso, Marcos, Marquez, Toribio, and Coutinho (7) convincingly argue that this similarity may be the cause of the decreased T4-cell functionality observed in AIDS and warn against the possible negative effects of vaccinations against HIV.

Hoffman et al. (8) derive from this similarity an idiotypic network model in which HIV and allogeneic stimuli may act synergistically to cause AIDS. By comparison, their theory is much more complicated than the CD4-like one, and it involves network mechanisms not apparent in the disease.

While I do agree that the MHC II–gp120 similarity is quite central and may be the cause of a cohort of other effects in AIDS, I believe that blocking T4-cell generation is both a more direct consequence of this similarity and the main cause of the most remarkable effect of AIDS—its characteristic T4 lymphopenia. Finally, our theory has the advantage of being simple and amenable to experimental testing.

[†]Extremely little is known about the expected lifetime of human T4 cells, but in absence of any information, assuming a uniform distribution of ages may be a reasonable choice. Having done this, though, it still remains unclear what the specific value for the average lifetime of T4 cells should be. Guesses and estimates (based on different methods) yield absolutely different values (some of which are as low as 2 or 3 days). Extrapolating from the average lifetime of mouse lymphocytes, Herman Eisen (personal communication) guesses a few years for unstimulated T cells. A 1964 study (5) leads to an estimate of 18 months. (Radiation treatment for cervical carcinoma created acentric chromosome fragments in lymphocytes of a group of 25 women. Lacking centromeres, these fragments could not be integrated in the DNA of daughter cells, a fact that enables one to keep track solely of radiated lymphocytes. It is of course unclear how the lifetime of these "altered" lymphocytes relates to that of normal ones.)

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