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fragmentation has occurred, the probability of detecting apoptosis in productively infected CD4+ T cells at any given time should be between 1 and 4% (0.5 h ÷ [48 h + 0.5 h] ≈ 1% and 2 h ÷ [48 h + 2 h] = 4%). Thus, it is not surprising that viral RNA (transcripts) are frequently observed in lymphoid cells where apoptosis has not yet been initiated[1].

Because of the lack of phenotypic analysis of apoptotic lymphoid cells, interpretation of Finkel *et al.* data in relation to the *in vivo* mechanisms of HIV disease, requires caution.

Certainly, the 'tap' (proliferative pool) and the 'drain' (cell death by apoptosis) of the CD4+ T-cell compartment are both wide open in HIV-infected individuals. On the assumption that the source feeding the 'tap' is not eternal, strategies aimed at inhibiting T-cell activation and apoptosis[5,6] and/or preventing *de novo* viral infection[2,3] (that is, 'plugging the drain') will benefit the patient's otherwise exhausted immune system.

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Finkel *et al.* reply —

We found that most apoptotic cells were uninfected, consistent with an innocent bystander mechanism of cell death. The numerical estimates of Lu & Andrieu support this interpretation. However, we disagree with their interpretation of the recent data of Wei *et al.*[2], who demonstrated: (1) rapid plasma viral RNA decline after initiation of effective antiviral therapy; (2) a two-fold rise in CD4+ T cells in the blood; (3) plasma virus mutations within two weeks; and (4) a lower rate and extent of viral mutations in peripheral blood mononuclear cells (PBMCs).

Wei *et al.* state that "the difference in life span between virus-producing cells and latently infected cells suggests that virus expression *per se* is directly involved in CD4+ T-cell destruction. The data do not suggest a bystander mechanism of cell killing..." In fact, our data directly refute their interpretation. Wei *et al.* assume that the source of plasma virus is CD4+ T cells. Yet, the source of plasma virus is unknown. It is possible that most of the circulating free plasma virus is synthesized in non-T-cell populations. Our data demonstrate that acutely infected dendritic cells are 100-fold more effective in disseminating HIV compared to acutely infected CD4+ T cells (unpublished data). They also assume that the numbers of CD4+ T cells increase in the presence of viral inhibitors due to decreased destruction in lymphoreticular organs. Since blood lymphocytes represent only ~2% of total body lymphocytes, the modest increase in CD4+ T-cell counts could be due to redistribution from lymphoid organs. Such a redistribution is known to occur in animal models as a result of changes in antigen load. Furthermore, quantitation of CD4+ T cells in blood reveals neither the HIV infection status of individual cells nor their life span. Consequently, Wei *et al.* cannot draw conclusions regarding the mechanism(s) of CD4+ T-cell death from their limited data. In contrast, our data provide a snapshot of infection status *in vivo* and shows the number of uninfected bystander cells undergoing apoptosis. Finally, Wei *et al.* also assume that the viral load declines in the presence of viral inhibitors because infected cells die. The observed kinetics of declining viral load can be modeled mathematically without invoking death of infected cells. To describe free virus at steady state:

$$[T = R - D]$$

where T denotes total free virus, R is virus released, and D is virus destroyed;

$$[R = \Sigma_{N=0}^{N=\text{Total infected cells}} V_N(t)]$$

where N is number of infected cells, V is virus released per cell and t is time;

$$V = \int_{t_0}^{t} P(t)dt$$

where P is production rate of virus per cell and t_0 is time of infection. The presumed effect of the viral inhibitors is to inhibit new infection, thus preventing the increase in N.

The subsequent decline in viral load can be explained in two ways. One, discussed by Wei *et al.*, is that infected cells die and therefore the number of cells producing virus decreases. This assumes that the rate of viral production, P, is approximately constant over the lifetime of the cell. A second interpretation is that P is a complex function which is high during early infection of a cell and decreases over time. If the viral production rate is heavily dependent upon new infection and the viral turnover rate is high (as suggested by Wei *et al.*), then with shutoff of new infection, the viral load will decline, even if the infected cells do not die.

Lu & Andrieu's estimate of the time required to detect apoptosis in acutely infected cells is based upon limited *in vitro* data that cannot be compared directly to our data. Also, since apoptotic cells can be scored in our assay after phagocytosis, it is the clearance rate which is of interest. Although a matter of debate, recent data argue that clearance of apoptotic (uninfected) cells in tissues requires up to 24 hours[7], in sharp contrast to the 0.5–2.0 hours assumed by Lu & Andrieu.

We propose another explanation for the lack of infected, apoptotic cells in the lymph nodes of infected individuals. It is known that dying T cells may home to other organs (for example, liver) before undergoing apoptosis[8]. Therefore, it is possible that infected, apoptotic cells are in lymphoreticular organs other than the lymph node. We are currently investigating this proposal.

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