at this current level was limited to a few minutes by the attainable temperature rise. Although this output is too small for most applications, the authors outline plans to increase the yield to a million neutrons per second, comparable to that of some commercial portable neutron generators. Nevertheless, even at the level already attained, there are laboratory uses, such as measuring neutron detector response or for student practical demonstrations, for which a simple, inexpensive, monoenergetic neutron source would be most valuable. ■

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HIV

Viral blitzkrieg

R. Paul Johnson and Amitinder Kaur

It takes years for AIDS to develop from the damage inflicted on the immune system by HIV or its simian counterpart. Surprisingly, as many as half of the body's memory T cells may die at a very early stage of infection.

HIV and the related simian immunodeficiency virus (SIV) cause AIDS by infecting the master regulatory cells of the immune system — T helper cells, better known as $CD4^+$ T cells. It is generally years before enough damage is done to this cellular army for full-blown AIDS to develop. Nevertheless, two reports in this issue[1,2] (pages 1093 and 1148) suggest that the outcome of the battle between SIV and its host may be determined by a dramatic opening salvo, in which the virus eliminates around half of the host's memory $CD4^+$ T cells within four days — thus setting the stage for a lengthy war of attrition.

$CD4^+$ T lymphocytes are so called because they express a receptor protein termed CD4; this is necessary for T-cell function, but has also been co-opted by HIV and SIV to gain entry to the cells. Previous results suggested that HIV/SIV replication is restricted to a relatively small fraction (0.01–1%) of $CD4^+$ T cells in the chronic stages of infection[3]. This low frequency of infection seemed to reflect the fact that the viruses require the presence of a co-receptor in addition to CD4 to gain entry, and also that they replicate best in activated memory $CD4^+$ T cells (memory cells being those previously stimulated by foreign antigen). The preferred co-receptor for most HIV and SIV strains is CCR5, which is expressed only in a subset of memory $CD4^+$ T cells.

Despite the apparent low frequency of T-cell infection in chronic infection, seminal studies in SIV-infected monkeys[4] — subsequently confirmed in HIV-infected humans[5,6] — revealed a rapid and widespread depletion of $CD4^+$ T cells in the gut (mucosal T cells) during the first few weeks of infection. T cells in the blood or lymph nodes did not show the same degree of depletion. This predilection of HIV and SIV for replicating in gut lymphocytes was felt to be a consequence of the relatively large populations of activated $CD4^+$ T cells at this site that express CCR5. However, the proportion of cells actually infected with SIV was not known; nor was it clear whether T-cell activation was in fact required for infection, or how T cells were killed.

Mattapallil *et al.*[1] have now examined the role of SIV in the depletion of $CD4^+$ T cells during early (acute) stages of infection. As previously reported[4], SIV rapidly depleted $CD4^+$ T cells in the gut. Remarkably, however, 60–80% of memory $CD4^+$ T cells were concurrently depleted at all sites. Using a technique that can detect a single copy of SIV DNA, the authors determined that 30–60% of all memory $CD4^+$ T lymphocytes were infected with SIV within 10 days of infection, regardless of their location, and that most of these cells had disappeared 4 days later. These percentages far exceed the number of $CD4^+$ T cells that express CCR5, but the authors propose that this apparent contradiction may be resolved by their finding of low levels of CCR5-encoding messenger RNA in memory cells in which CCR5 protein could not be detected by flow cytometry. This implies that such cells may in fact express sufficient levels of CCR5 protein to render them permissive for SIV infection. Alternatively, SIV may be entering the cells using other co-receptors.

Li and colleagues' paper[2] provides a complementary perspective on this viral blitzkrieg. By identifying cells expressing SIV RNA in tissue sections, these investigators characterized the activation state of virus-producing cells (viral production requires SIV DNA to be transcribed into RNA). Consistent with their earlier work[7], they found that most infected cells did not express markers of activation (CD25 or CD69), nor did they express Ki67 — a molecule found in

Behavioural ecology

Cue for kin

If you yourself can't breed, you can at least help your relatives with their offspring. Such altruistic behaviour occurs in long-tailed tits (*Aegithalos caudatus*, pictured), which Stuart Sharp and colleagues have studied to find out what cues enable a 'helper' to recognize kin. Their report appears elsewhere in this issue (*Nature* **434,** 1127–1130; 2005).

Adult long-tailed tits pair off and attempt to breed each year, but many don't succeed because of high rates of predation on the eggs or nestlings. The childless parents may then turn to assisting kin in feeding their brood — which makes sense in evolutionary terms but requires some form of recognition system. Long-tailed tits are not the greatest of vocalists. They sing infrequently but do have an individually characteristic contact call, the 'churr', which develops even before fledging and is retained in the adult bird.

The first part of Sharp and colleagues' research involved the playback to individuals of churr calls belonging to a close relative and a non-relative, and a further two trials in which the frequency of these calls had been tweaked. The responses of birds to the untweaked calls of relatives differed significantly from their responses to the other three calls. From this, the authors conclude that the churr call provides cues involved in kin recognition.

The most innovative part of the study, however, was an investigation into how much churr acquisition owes to nurture (learning) and nature (genetics). This took the form of swapping young birds between nests, so that adult birds were raising foster nestlings along with their true offspring. The churr calls of the fostered birds were the same as those of their nestmates, and unlike those of their biological siblings raised elsewhere — so it seems that the churr is in large part learned.

The pattern of helping observed in long-tailed tits is consistent with the use of this learned cue in the great majority of cases. But this kin-recognition system evidently isn't faultless: in 6% of cases, an adult helped unrelated nestlings. As the authors point out, recognition systems are rarely perfect. **Tim Lincoln**

ANDREW MACCOLL

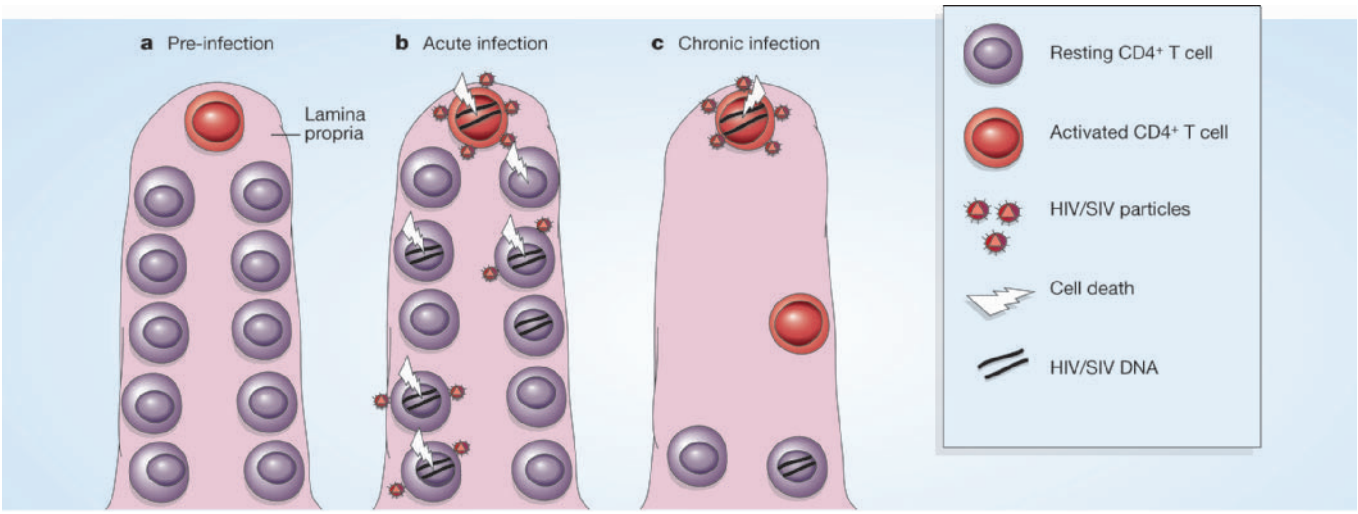

Figure 1 **Model for the depletion of gut CD4-expressing T lymphocytes by SIV. Most of the body's memory CD4$^+$ T helper cells are found in the gut, mainly in a compartment known as the lamina propria.** a, **Before infection, non-dividing (resting) CD4$^+$ T cells in the lamina propria outnumber activated T cells by 70-fold or more.** b, **In the initial (acute) phase of infection, the CD4$^+$ T-cell population in the gut is eliminated rapidly; the new papers reveal that up to 60% of these T cells are infected with SIV[1] and that most of the infected cells are resting rather than activated[2]. Only a subset of infected cells that contain SIV DNA will express SIV RNA and produce viral particles. Such 'productively infected' cells, cells that contain viral DNA but not RNA, and uninfected cells may all be killed as a result of SIV infection, although the relative numbers of each are not known.** c, **During chronic infection, in response to the depletion of resting cells, the number of activated cells increases slightly. These cells now represent the dominant site of viral replication.**

cells that have recently divided. Hence, these cells were deemed to be 'resting'.

Although these resting cells produce less virus than do Ki67-expressing cells, they vastly outnumber their activated counterparts and so serve as the major viral reservoir during this first phase of infection. Because of its ability to replicate in non-dividing cells, SIV can broaden its substrate base significantly, and deplete most CCR5$^+$ CD4$^+$ T cells in all lymphocyte compartments during acute infection. Once the resting memory-cell population is nearly eliminated, the activated population increases slightly, but now makes a larger contribution to total virus production (Fig. 1).

The idea that SIV (and presumably HIV) can infect resting lymphocytes seems to contradict the conventional wisdom that these viruses replicate primarily in activated cells. But mucosal lymphocytes (the main target cells) are probably better described as 'recently activated' rather than truly resting. Many such cells appear to be derived from blood cells that have recently divided and then migrated into the mucosa, where they lose Ki67 expression[8]. The dichotomous nomenclature of 'resting' and 'activated' T cells may obscure our ability to understand the range of cellular states that affects SIV/HIV replication. Further research is needed to determine the roles of viral proteins, host cytokine proteins, nucleotide pools and cellular resistance factors[9,10] in regulating viral replication in non-dividing lymphocytes.

Although there are many points of agreement between the new papers[1,2], they differ on a key issue: the relative roles of direct versus indirect killing (death of virus-infected versus uninfected cells). Mattapallil and colleagues' finding[1] of SIV DNA in up to 60% of memory CD4$^+$ T cells at peak suggests that nearly all T-cell death at early stages can be attributed to direct infection. But Li *et al.*[2] found a significantly lower peak frequency of cells expressing SIV RNA, and suggest that indirect mechanisms (mediated by the Fas–FasL cell-suicide pathway) also contribute to T-cell death in acute infection.

Differences in the sensitivity of the techniques used by the two groups to detect infected cells may contribute to this discrepancy. But another, perhaps more likely, possibility is that not all of the cells that contained SIV DNA were producing new viruses (indicated by the presence of SIV RNA). A similar situation occurs in chronic HIV infection, where fewer than 1 in 100 infected cells is 'productively infected'[3].

Do these acute events determine the chronic course of infection? Owing to their focus on acute infection, neither study[1,2] allowed early events to be correlated with disease progression. So it is not known whether differences in the proportion of SIV-infected CD4$^+$ T cells — or in the size of the memory T-cell pool destroyed during peak replication — affect the extent of virus production during chronic infection, a key predictor of disease progression. The contribution of immune responses to the depletion of infected CD4$^+$ cells and the initial drop in peak viral load also remains controversial.

However, once acute viral replication has subsided, different viral and T-cell dynamics will come into play. Overall levels of virus production will fall, even though the shift in viral replication from resting to activated T cells means that more viruses are produced per cell. The smaller size of the infected T-cell pool and the generation of virus-specific immune responses are both likely to contribute to the overall decrease in virus production. The body's ability to regenerate mucosal lymphocyte pools is also likely to be important in forestalling the onset of AIDS[8].

As for vaccines, the findings reinforce the rationale for blocking HIV before it gains access to the fertile grounds of mucosal lymphocytes — and for reducing the initial burst of viral replication. Recent vaccine efforts have been aimed at activating other T cells, those expressing CD8, which are most effective in decreasing chronic levels of viral replication and slowing down disease progression[11]. But it may be more effective to stimulate the body to produce neutralizing antibodies that prevent the initial burst of replication — although this remains a challenge. ■

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