degrees of affinity (**Fig. 1a**), they found a sharp difference between LFA-1 activation by soluble versus immobilized chemokines. Indeed, soluble chemokines, although able to trigger the LFA-1 high-affinity state, failed to induce a conformation corresponding to intermediate affinity. The authors show that the intermediate-affinity state of LFA-1 is induced only by immobilized chemokines and is essential for supporting interaction with ICAM-1 under flow. Then the authors provide evidence showing that after interaction with ICAM-1, LFA-1 is driven to a high-affinity state by an outside-in mechanism that definitively stabilizes cell adhesion under flow (**Fig. 1b**). The authors conclude that in physiological situations (flow conditions), what it is critical to LFA-1-mediated adhesion in rolling lymphocytes is not a progressive global signal but instead is the concurrent, spatially restricted, engagement of chemokines and ICAM-1, which leads to a concurrent integration of inside-out and outside-in signaling events. Thus, these data suggest that stepwise LFA-1 triggering is not necessary. Notably, according to this model, the presence of flow dictates the modality of LFA-1 activation supporting lymphocyte arrest: adhesion under flow is possible only if LFA-1 is triggered, by chemokines, to an intermediate-affinity state.

The authors speculate that their model, by temporally and spatially restricting LFA-1 activation to the site of interaction with ICAM-1, avoids the risk of random integrin activation on the cell surface, which could lead to cell aggregation. But there is another reason that this model seems satisfactory. Leukocyte recruitment is a specific process. Diversity depends on both qualitative and quantitative factors[10,11]. For example, chemokine and chemokine receptors participate in diversity generation by means of differential expression on the endothelium and on leukocytes, respectively. If LFA-1 activation is a progressive process, it might be expected that, independent of the density of endothelial chemokine and of the abundance of chemokine receptor expressed by the leukocyte, activation of leukocyte arrest is simply a matter of time. Indeed, the leukocyte needs to roll only long enough to reach a defined threshold of proadhesive signal. Thus, leukocytes expressing suboptimal levels of chemokine receptors could still be able, over time, to activate integrins and adhere. But this could easily alter the mechanism controlling the diversity of leukocyte recruitment, which is based on the differential expression of molecules, with adverse consequences for the coherence of the immune response. Thus, the model proposed by Shamri and colleagues seems more adequate for maintaining the specificity of the immune response.

At present it cannot be determined whether this model will hold for other integrin subtypes and in any 'physio-pathological' situation. Selectin-derived signaling events should be also taken in account, and this could challenge the model[12]. Furthermore, it will be useful to test the model in different leukocyte subtypes. Another important issue to resolve is why soluble versus immobilized chemokines trigger different LFA-1 affinity states. This corresponds to asking why a global versus spatially restricted signal transduction leads to different mechanisms of LFA-1 activation. This could be due to quantitative aspects in signaling events and could indicate that the equilibrium between different LFA-1 conformational states is influenced by the amount of signal transduction. But it is also possible that a spatially restricted signaling event leading to LFA-1 activation is qualitatively different from a global signal. These are still minimally appreciated aspects of the complexity of signaling networks triggered by chemokines, and their understanding will be a relevant challenge for the future.

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HIV pathogenesis: the first cut is the deepest

Louis J Picker & David I Watkins

HIV pathogenesis is thought of as a chronic infection involving slow degradation of immunity that ultimately leads to AIDS. This scenario, however, could reflect the decay of an immune system mortally wounded during acute HIV infection.

Studies using the simian immunodeficiency virus (SIV)–infected rhesus monkey model of AIDS, capped by two papers in a recent issue of *Nature*[1,2], have begun to shed new light on how human immunodeficiency virus (HIV) causes immune deficiency. These emerging data demonstrate that AIDS is really a 'tale of two infections': a highly destructive acute infection in which the virus massively depletes the $CD4^+$ memory T cell compartment, and the more familiar chronic phase in which a likely crippled immune system slowly dies.

Progressive cellular immunodeficiency underlies AIDS, but the pathogenic sequence linking viral replication to immune deficiency has remained controversial[3,4]. The early realization that HIV directly targets $CD4^+$ T cells led to the hypothesis that $CD4^+$ T cell destruction results in the loss of critical immune effector and/or regulatory functions, ultimately leading to immune deficiency. However, subsequent observations, including the relative paucity of infected $CD4^+$ T cells in the chronic phase, the slow loss of $CD4^+$ T cells and the long delay (years) between infection and symptomatic immune deficiency, all in the face of continuous, high-level viral replication, were difficult to reconcile with this direct $CD4^+$ T cell destruction hypothesis. To accommodate those observations, a variety of indirect pathogenic mechanisms have been invoked, including bystander apoptosis, functional exhaustion and gradual loss of T cell–regenerative capabilities, but so far the relative contribution of these mechanisms to the pathogenic sequence has not been definitively established.

A new view of AIDS pathogenesis began to evolve several years ago when it was first noted that monkeys infected with SIV lost almost their entire complement of $CD4^+$ T cells in the

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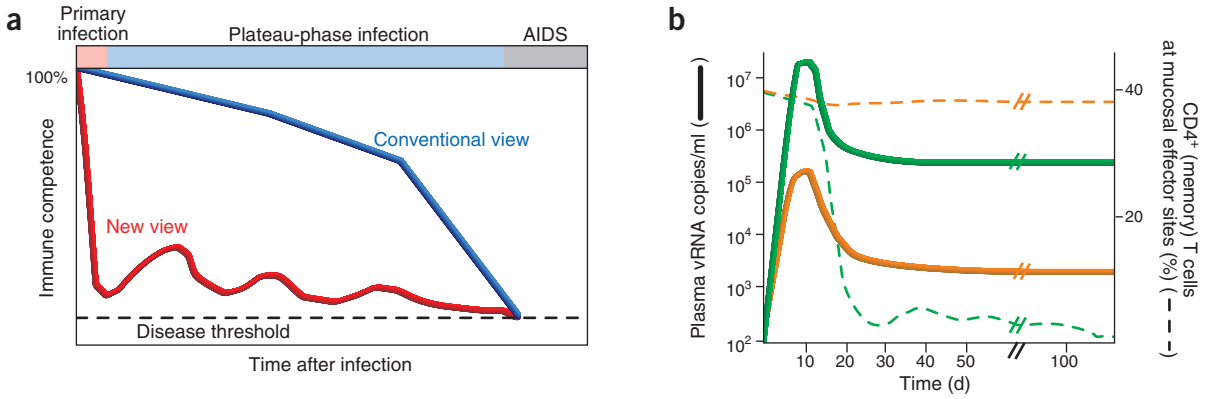

Figure 1 New view of SIV/HIV pathogenesis and the implications for vaccine development. (**a**) Conventional view of a gradual decrease in immune competence (blue line) contrasted with the new view (red line), in which the most destructive insult takes place in acute infection. (**b**) SIV infection causes an immediate decrease in memory CD4+ cells (dashed green line), with viral loads (solid green line) peaking at more than 1×10^7 copies/ml, eventually establishing a set point of between 1×10^5 and 1×10^6 copies/ml. The goal of a vaccine should be to prevent destruction of the memory CD4+ cells (dashed orange line). A reduction in peak viral load (solid orange line) to less than 5×10^5 copies/ml should prevent loss of memory CD4+ T cells. Vaccine-induced control of viral replication to a set point of less than 5×10^3 copies/ml would represent a reduction in the set point of 1.5–2 log, roughly paralleling a reduction in the median set point in humans from 30,000 to 1,500 copies/ml. People with viral loads of less than 1,500 copies/ml do not transmit HIV[13]. vRNA, viral RNA.

intestinal lamina propria[5]. Subsequent studies demonstrated that this effect was a function of the CCR5 tropism of SIV and that most CD4+ memory T cells inhabiting the intestinal mucosa (and other mucosal sites) are CCR5+ (refs. 6,7). These observations remained somewhat in the background until last year, when two papers demonstrated the same phenomena in humans infected with HIV[8,9]. Now both Mattapallil *et al.*[1] and Li *et al.*[2] have documented massive infection of intestinal lamina propria CD4+ T cells in rhesus monkeys infected with CCR5-tropic SIV, peaking at day 10 after inoculation. Using quantitative PCR analysis of sorted cells, Mattapallil *et al.* estimate infection frequencies among mucosal CD4+ T cells to be in the range of 60%. They suggest that direct viral infection with cell destruction via either viral or cytotoxic T cell–mediated cytolysis accounts for the observed CD4+ T cell depletion in these sites. These investigators also documented high rates of infection among CD4+ memory T cells in other sites, emphasizing the systemic nature of this target cell destruction. Li *et al.* focused on the colon, using quantitative *in situ* hybridization to demonstrate peak infection rates of about 7% of CD4+ T cells. They calculated that only 20% of the depletion could be accounted for by direct infection. These investigators found extensive CD4+ T cell apoptosis associated with marked upregulation of Fas and Fas ligand and proposed that exposure of CCR5+CD4+ T cells to high local concentrations of SIV envelope protein (Env) initiated Fas-mediated apoptosis.

Together these papers document massive destruction of the CD4+ memory compartment in acute SIV infection, particularly in mucosal effector sites, mediated by direct productive infection and Env-induced apoptosis. Both papers also show that the frequencies of infected cells precipitously drop after day 10 of infection, concordant with loss of susceptible target cells. Other work has demonstrated that SIV infection induces a state of intense immune activation and a marked upregulation of CD4+ memory T cell proliferation and turnover, including new CCR5-expressing CD4+ memory cells[7]. In keeping with this, Li *et al.* also document a switch from high-frequency infection of resting T cells to low-frequency infection of activated T cells. These findings are in agreement with previous observations showing that most CCR5-expressing CD4+ memory T cell targets are actively dividing cells in the stages of SIV infection after the acute stage[7]. These changes are precisely aligned with the drop in plasma viral load after the peak to a stable plateau, suggesting that SIV-specific CD8+ T cell responses are not the sole determinant of the characteristic SIV viral dynamic patterns. Instead, the nature, frequency and regenerative capacity of susceptible target T cells are probably also important in determining the prognostically important viral set point.

The effect of these substantial changes in CD4+ memory T cell dynamics on immune competence is profound. After infection, a generalized CD4+ memory T cell proliferative response produces short-lived, mucosal tissue–homing CD4+ memory cells that partially compensate for the acute loss of the mucosal CD4+ memory compartment[7]. However, this response is incomplete and prone to failure. Early loss of this proliferative response results in the cessation of new CD4+ memory T cell emigration into tissues and is strongly associated with fatal rapid progression[7]. In monkeys surviving into the chronic phase of SIV infection, new CD4+ memory T cell production may partially restore mucosal CD4+ memory T cell populations, but this restoration is almost always transient. By 1 year after infection, most 'normal progressor' animals establish a quasi-stable steady state, with CD4+ cells constituting only 1–3% of mucosal T cells. Notably, clinically overt immune deficiency seems to mostly, if not exclusively, occur in monkeys with profound mucosal CD4+ T cell depletion, with those monkeys manifesting less than 0.5% mucosal CD4+ T cells at highest risk (L.P., unpublished data). Thus, although it is very likely that immune exhaustion and/or other immune dysregulation contribute to opportunistic infection susceptibility, the common denominator of overtly immunocompromised SIV-infected monkeys is massive CD4+ memory depletion in mucosal effector sites, a state that initiates in the first 21 days of infection.

The early destruction of the CD4+ memory compartment is likely to result in considerable subclinical effects as well. A substantial reduction in the immunologic resources at tissue-environmental interfaces might increase the frequency and intensity of local pathogen growth and invasion, perhaps contributing to the chronic immune hyperactivation and microenvironmental destruction associated with progressive infection[3,4]. Although HIV- or SIV-specific CD4+ T cells can develop in untreated infection, those populations are selectively targeted by virus[10]. Thus, antigen-specific CD4+ T cell support for effective CD8+ CTL responses is acutely compromised and chronically depleted.

These new observations suggest that conventional views of HIV and SIV pathogenesis should be revised. Contrary to previous views

of the development of overt immune deficiency, in which immune competence was thought to slowly degrade, it is likely that the enormous viral replication and extensive $CD4^+$ memory T cell destruction during acute infection cripples the immune system at the outset of infection and sets the stage for its eventual failure. The chronic phase would therefore represent a period of increasingly less effective compensation accompanied by further erosion of immune responsiveness by chronic activation-mediated dysregulation and micro-environmental destruction, ultimately degrading immune competence below the threshold required to keep opportunistic pathogens at bay (**Fig. 1a**).

This new view of pathogenesis has serious implications for HIV therapy and vaccine development. For the former, emerging data in both humans and monkeys suggest that even with effective viral suppression, reconstitution of the mucosal $CD4^+$ T cell compartment is incomplete, slow and variable (refs. 8,9 and L.P., unpublished data). Thus, full restoration of normal immune competence in HIV^+ subjects will probably require more than antiretroviral therapy alone. Perhaps efforts toward understanding the mechanisms of $CD4^+$ memory regeneration need to be redoubled. From a vaccine development perspective, it is clear that viral replication must be constrained early, before massive systemic infection of $CCR5^+CD4^+$ memory T cells. It is unreasonable to expect effective control of viral replication once these key cells are destroyed. Our own experience with SIV-infected monkeys suggests that peak acute plasma viral loads of less than 5×10^5 are compatible with preservation of $CD4^+$ mucosal memory compartments and subsequent control, whereas plasma viral loads above this will probably lead to vaccine failure (**Fig. 1b**). In humans, these thresholds may be different, but it is likely that the same rules apply.

In the end, this is yet another story about the incredible adaptation of SIV and HIV; in this case, the 'choice' of the CCR5 coreceptor. By targeting this molecule, the virus has access to high-density targets, both at sites of entry and systemically, allowing massive viral replication at the outset of infection. This facilitates the all-important generation of viral diversity, resulting in rapid viral adaptation to the individual host's environment. Targeting $CCR5^+CD4^+$ memory T cells, the tissue effector cells of this lineage, also undoubtedly results in an immune deficit. This facilitates viral avoidance of host adaptive immunity but at the same time leaves intact a tremendous (central memory) regenerative capacity that is programmed to generate additional CCR5-expressing targets. As the virus stimulates this regenerative machinery, it creates its own targets and avoids the consequences of target cell depletion. Moreover, because of the enormous resilience of the cellular immune system, this cycle continues for long periods, facilitating infection of new hosts, until ultimately (inevitably) immune competence drops below a certain threshold and overt disease ensues. It is noteworthy that in the relatively apathogenic, 'natural' SIV infections of African monkeys, the hosts do not control viral replication but instead have downmodulated both CCR5 expression on mucosal $CD4^+$ T cells and immune activation[11,12]. These African monkeys may therefore avoid the extensive mucosal depletion and downstream pathogenic effects of SIV infection by interfering with this unique CCR5-centered adaptation of the virus, a strategy that might prove fruitful to mimic in the search for new approaches to AIDS therapy.

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Resolving a case of split personality

David B Corry

The function of prostaglandin E_2 in allergy has long been ambiguous. Now a comprehensive assessment of prostaglandin E_2 receptor–deficient mice demonstrates the main anti-inflammatory function of this prostaglandin in allergic lung disease.

In asthma, prostaglandins generally function as proinflammatory molecules, but studies of prostaglandin E_2 (PGE_2) have produced conflicting results, demonstrating either pro- or anti-inflammatory effects depending on the experimental context. The study by Kunikata *et al.* in this issue of *Nature Immunology*[1] uses unusually robust methods to help resolve longstanding issues regarding the biology of this important prostaglandin. The prostaglandin receptors are named for the letter of the prostaglandin series; for example, E prostaglandin (EP) receptor. Unique among the prostaglandins, PGE_2 signals through four distinct receptors. The authors demonstrate clearly that lack of a single receptor subtype, EP3, results in accelerated allergic inflammation in mice and that stimulation of the same receptor inhibits expression of proallergic genes. These findings suggest new hypotheses regarding how prostaglandins regulate allergic inflammation and reinvigorate the idea of prostaglandins as therapeutic agents in atopic disease.

Since their initial discovery more than 70 years ago, the prostaglandins have been studied extensively as mediators of diverse physiological processes, work that culminated in the Nobel Prize in physiology or medicine in 1982. Far from waning, work on the prostaglandins, named for the prostate gland that secretes copious quantities of these potent biological chemicals, has only accelerated since then. The prostaglandins are now recognized as chief regulators of vascular tone, reproduction, inflammation, pain, central nervous system function, and renal, pulmonary and endocrine physiology. In addition, the prostaglandins have been linked to the pathogenesis of some cancers. Like the leukotrienes, which also have much relevance to allergic inflammation, the five prostaglandins of greatest medical importance are the products of arachidonic acid metabolism (**Fig. 1**).

PGE_2 has diverse and often notably contradictory associations with allergic phenomena, making generalizations as to its function in allergy difficult to formulate. PGE_2 is found

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