Host factors and the pathogenesis of HIV-induced disease

Anthony S. Fauci

The level of human immunodeficiency virus (HIV) replication in patients reflects a balance between stimulatory and inhibitory host factors (particularly endogenous cytokines). New information concerning the cellular co-receptors for HIV and the cellular tropism of different strains of virus will advance our understanding of HIV-induced pathogenesis and suggests new therapeutic and preventive strategies.

THE pathogenesis of HIV-induced disease is complex and multifactorial[1,2]. Following primary infection with HIV, a burst of virus replication disseminates the virus to lymphoid organs[1]. A robust cellular and humoral immune response usually inhibits viral replication within weeks[3–6] but the virus almost invariably escapes from immune containment, producing a chronic, persistent infection, leading to advanced clinical disease with a strikingly high mortality over a median period of about 10 years (ref. 7). Some viral replication occurs in lymphoid tissue (and perhaps elsewhere, for example in the brain) throughout the entire course of infection, even when the patient is clinically asymptomatic[8]. Indeed, sensitive techniques for detecting viral RNA reveal virus in the plasma at every stage of disease[9]. Although at any point in the infection, plasma viral levels are apparently stable, the virus is in fact turning over very rapidly[10,11], and $\sim 10^{10}$ virons are produced and cleared from the circulation each day[12,13]. More than 99% of virus is thought to be produced by newly infected $CD4^+$ T cells, whose half-life is 1.6 days (refs 10–12).

The steady-state level of plasma viraemia from about 6 months after infection strongly predicts how fast the disease will progress[14] and has considerable pathophysiological significance. It is influenced by both host and viral factors. Among the latter are replicative fitness, predeliction for mutation, and cytopathicity[13,15], all of which are important components of any model of HIV pathogenesis. This review, however, will focus on the role of host factors, particularly cellular activation and the role of cytokines and their receptors in regulating viral replication and in pathogenesis. Clearly, the immune response to HIV also affects the progress of the infection. This issue has recently been reviewed[16] and will not be addressed here; instead, I will focus on the way in which the balance between HIV-inducing and HIV-suppressing host factors controls the net level of viral replication. Perturbation of this balance both *in vitro* and *in vivo* strongly affects the net replication of HIV and can significantly influence the course of disease (Fig. 1).

Exogenous factors and HIV replication

HIV replicates more efficiently in activated cells[17–20], and viral levels consistently increase when the immune system of HIV-infected individuals is activated by exogenous stimuli such as opportunistic pathogens[21–25]. Active infection by *Mycobacterium tuberculosis*, for instance, substantially increases plasma viraemia, which returns to baseline when the infection is successfully treated[22]. This increase in the rate of viral replication is associated with cellular activation and expression of HIV-inducing cytokines, as well as an acceleration in the course of HIV-induced disease[26,27] (see below). Similarly, the course of HIV infection appears to be more aggressive in sub-Saharan Africa than in developed countries[28–31], probably reflecting the immune activation associated with frequent and chronic infection by parasites and other pathogens[28,32]. This immune activation is associated with elevated levels of HIV-inducing cytokines such as TNF-α and interleukin (IL)-1β and IL-6 (refs 33, 34).

The impact of immune activation on viral replication and disease progression has been confirmed and expanded in experimental studies of simian immunodeficiency virus (SIV)-infected monkeys and HIV-infected chimpanzees and humans[35–37]. HIV-infected individuals manifest transient bursts of viraemia on immunization with antigens such as influenza and tetanus toxoid[35–38], and peripheral blood mononuclear cells (PBMCs) obtained from such individuals during the transient period of cellular activation following immunization support greater HIV replication *in vitro*[37]. Immunization with tetanus toxoid also renders PMBCs from uninfected individuals more susceptible to infection with HIV *in vitro*[37]. Exogenous factors thus play a major role in regulating viral replication, predominantly by perturbing cellular activation and cytokine production.

Endogenous cytokines

The immune system is regulated by a complex network of pleiotropic and redundant cytokines, which are continually secreted to a greater or lesser degree even when the system is apparently quiescent, and are further expressed to varying degrees in response to antigen[39]. As HIV directly infects cells of the immune system and triggers a robust immune response, it is an important and persistent source of immune activation[1]. This activation is intimately linked to cytokine secretion[39], and expression of several cytokines is enhanced in HIV-infected individuals. Secretion of the proinflammatory cytokines TNF-α, IL-6 and IL-1β is increased in PBMCs[40], and expression of these cytokines together with interferon (IFN)-γ is greatly increased in lymphoid tissue[40,41]. Elevated levels of TNF-α and IL-6 are also found in the plasma and cerebrospinal fluid[40].

Cytokine patterns have been linked to a polarization of the cell-mediated and humoral immune responses[42]. T-helper (Th)-1 cells are characterized by secretion of IL-2 and IFN-γ, and favour cell-mediated immune responses; Th-2 cells are characterized by secretion of IL-4, IL-5 and IL-10, and favour humoral immune responses[42,43]. Although an imbalance in subsets of $CD4^+$ T lymphocytes has been reported in HIV-infected individuals, with disease progression reflecting a transition from Th-1 to Th-2 cytokine patterns[44,45], this has been disputed[41,46]; in humans several other cell types secrete these cytokines[41], further confusing the issue. The subject has been discussed in detail elsewhere[42,43], and is beyond the scope of this review.

The finding that crude supernatants from PBMC cultures induce viral expression in chronically infected cell lines[47] led to the discovery that numerous individual cytokines induce HIV expression either when manipulated endogenously or when added to acutely or chronically infected cell cultures[40]. Such cytokines include IL-1β, IL-2, IL-3, IL-6, IL-12, TNF-α and TNF-β, and colony-stimulating factors M-CSF and GM-CSF. IFN-α and

IFN-β suppress HIV replication, whereas TGF-β, IL-4, IL-10, IL-13 and IFN-γ either induce or suppress HIV expression, depending on the culture system[40]. Several of the active cytokines are synergistic, whereas others exert their effects in an autocrine and paracrine manner in the same way that they control the immune system[40]. Both the *in vitro* study of PBMCs acutely infected with HIV and studies of PBMCs and lymph-node mononuclear cells from HIV-infected individuals indicate that HIV replication is tightly controlled by these cytokines. The blockade of cytokines such as TNF-α, IL-1β and IFN-γ by receptor antagonists, or by antibodies against the factors or their receptors, consistently and occasionally completely suppresses viral replication[48,49].

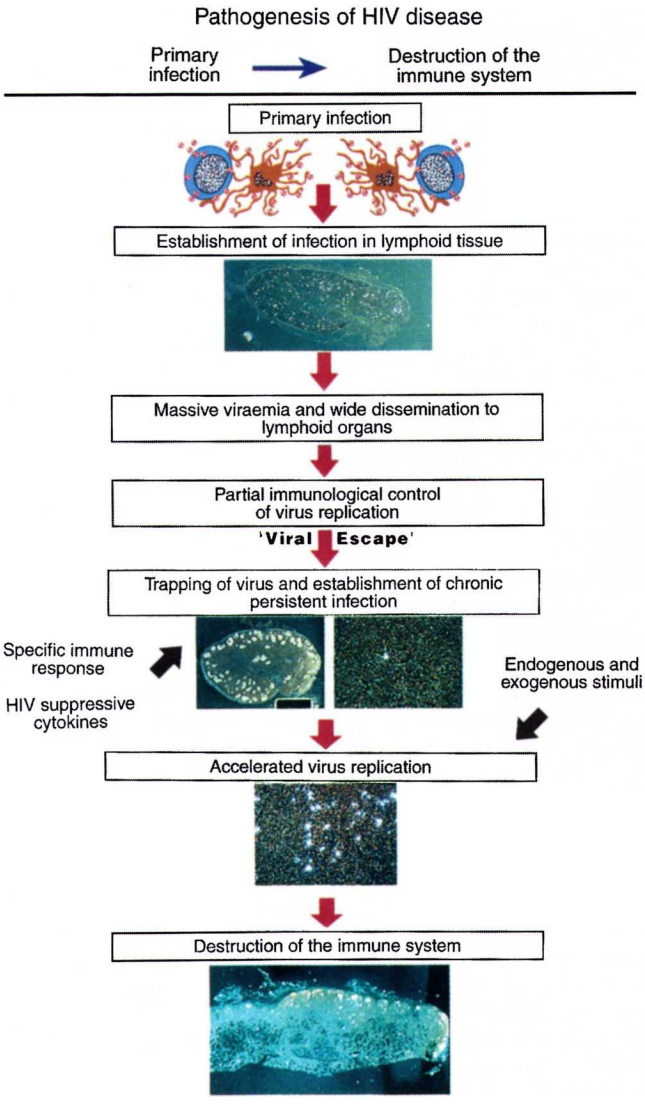

FIG. 1 Pathogenic events in HIV disease. On entry into the body, HIV probably encounters a dendritic cell, which is either infected or carries the virus to a $CD4^+$ T cell in a lymphoid organ. Infection is then established in the lymphoid organ and a burst of viraemia seeds virus throughout the body. Viral replication is partially controlled, but the remaining replication almost invariably leads to escape from immune control, and establishment of chronic persistent infection in lymphoid tissue. The net level of viral replication is regulated by a balance between factors that induce virus replication and factors that contain or suppress it. In most patients, replication accelerates over a period of time, leading to the destruction of the immune system. The white dots in the lymphoid tissue represent individual cells expressing HIV viral RNA, as determined by *in situ* hybridization. Trapped virus (large clumps of white staining in the peripheral regions of the lymph node) is extracellular.

Another example of the effects of endogenous cytokines on HIV replication is that of IL-10, an immunosuppressive cytokine that inhibits HIV replication in acutely infected monocyte/macrophages by blocking secretion of the HIV-inducing cytokines TNF-α and IL-6 (ref. 50). *In vivo* infusion of a single bolus of IL-10 into normal individuals renders their cells unable to secrete cytokines in response to lipopolysaccharide and makes them relatively resistant to *in vitro* infection with HIV (A.S.F., D. Weissman, unpublished observations). In preliminary studies of HIV-infected individuals, a similar bolus dramatically decreased plasma viraemia for several hours, during which time their cells could not be induced to secrete TNF-α or IL-1β *in vitro* (A.S.F. and D. Weissman, unpublished observations).

The molecular mechanisms by which these cytokines affect HIV replication are best understood for TNF-α, arguably the most important and certainly the most potent of the HIV-inducing cytokines[40]. TNF-α activates the cellular transcription factor NF-κB, which induces expression of numerous cellular genes[51]. Binding sites for NF-κB occur within the long terminal repeat (LTR) of the HIV genome, and the effects of TNF-α on HIV are mediated by NF-κB-induced transcription[52,53]. Although IL-1β is also thought to affect viral transcription, it is unclear whether NF-κB is involved[40]. Other cytokines, such as IL-6, GM-CSF and IFN-γ, have predominantly post-transcriptional effects[40].

Suppression of HIV replication

The effects of HIV-stimulating cytokines are counterbalanced by those that suppress HIV replication. An initial report of non-cytolytic suppression of HIV replication by $CD8^+$ T cells[54,55] was subsequently shown to reflect the action of a soluble factor whose precise identity remains unclear[55]. The phenomenon has since been corroborated by several laboratories[55], however, and multiple suppressor factors whose activities can be distinguished in various *in vitro* models of HIV replication have now been identified[56–58].

The search for the identity of these factors has now triggered a new area of HIV research. In late 1995, Cocchi *et al.* showed that the suppressive effects of supernatants from $CD8^+$ T cells transformed with human T-lymphotropic virus (HTLV)-1 or from HIV-infected individuals were due to the chemoattractant cytokines (β-chemokines) RANTES, MIP-1α and MIP-1β (ref. 58). The suppressive effects were observed in acute infections with some but not all strains of HIV-1, a dichotomy that was then unexplained. Although the β-chemokines were clearly the predominant suppressive factors secreted by $CD8^+$ T cells in these experiments, they could not account for all of the suppressive effects mediated by $CD8^+$ T-cell supernatants in other systems. In cultured macrophages, the β-chemokines did not suppress acute infection[59,60], whereas supernatants from $CD8^+$ T cells did[60]. Moreover, $CD8^+$ T cells are not the only mononuclear cells that secrete RANTES, MIP-α and MIP-1β (ref. 61). Indeed, HIV replication in cultures of CD8-depleted PMBCs from HIV-infected individuals has been shown to reflect the balance of endogenous HIV-inducing and HIV-suppressing cytokines[49]. When the most potent HIV-inducing cytokines, such as TNF-α and IL-1β are neutralized, viral replication is markedly decreased, and when the β-chemokines RANTES, MIP-1α and MIP-1β are neutralized in the same cultures, viral replication is increased. Addition of autologous $CD8^+$ T cells to these cultures suppresses viral replication, but this suppression can only be overcome by neutralizing the β-chemokines when very low numbers of $CD8^+$ T cells are added[49], indicating that the $CD8^+$ T cells produce further unidentified HIV-suppressor factors. The steady state of HIV replication thus reflects the actions of various endogenous cytokines derived from multiple cell sources and can be affected by modulating these cytokines (Fig. 2).

Viral co-receptors and cellular tropisms

The ability of HIV-1 to infect different types of cells varies from

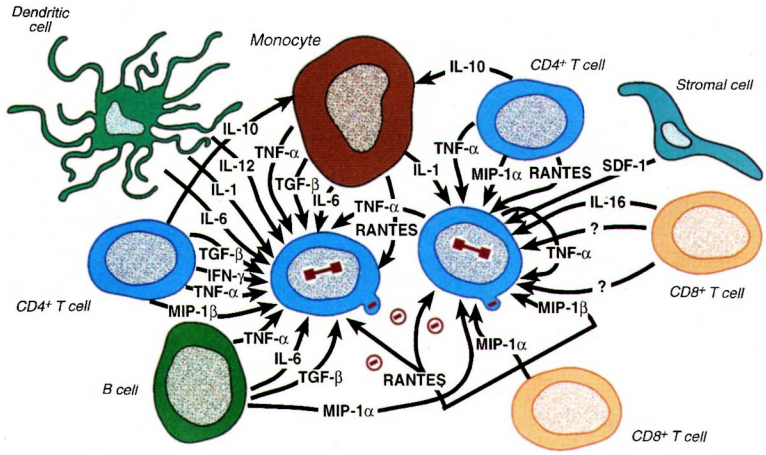

FIG. 2 Endogenous cytokines regulating viral replication in $CD4^+$ T cells. Numerous cytokines, particularly the proinflammatory cytokines TNF-α, IL-1β and IL-6, strongly upregulate replication. TGF-β and IL-10 downregulate it—in IL-10's case, at least in part, by downregulating proinflammatory cytokines. The β-chemokines, which are secreted by a variety of cell types including $CD8^+$ and $CD8^-$ mononuclear cells, strongly inhibit infection by M-tropic strains of HIV-1, whereas SDF-1 inhibits infection with T-tropic strains.

isolate to isolate and is referred to as cellular tropism. All strains of HIV infect primary $CD4^+$ T lymphocytes. Many primary isolates also replicate well in monocytes, but not in transformed T-cell lines[62], and are classified as monocyte-or macrophage-tropic (M-tropic), although they can also infect primary T cells. Other isolates, particularly those that have been passaged in lymphoid cells *in vitro* (T-cell-line-adapted strains), infect primary T lymphocytes but not monocytes or macrophages, and are referred to as T-cell-tropic (T-tropic) viruses. As HIV infection progresses, the initially dominant M-tropic viruses are usually replaced by T-tropic viruses[63–65]. The former are generally found not to induce syncytia formation *in vitro*, although the latter do[66,67], and the terms M-tropic and non-synctia-inducing (NSI) or T-tropic and synctia-inducing (SI) are often used synonymously. This may not be entirely correct, as the transition from M-tropic/NSI to T-tropic/SI viruses as disease progresses may produce dual-tropic viruses that are M-tropic, despite SI characteristics[68–70]. The viral determinant of cellular tropism maps to the gp120 subunit of the HIV-1 Env protein, particularly the third variable region or V3 loop of gp120 (ref. 71, see below). Studies to delineate the basis of cellular tropism led to the identification of the first bona fide co-receptor for HIV-1.

In early 1996, Feng *et al.* reported that the receptor CXCR4 (also termed fusin or LESTR) was the co-receptor responsible for the efficient entry of T-tropic strains of HIV-1 into target cells[72]. CXCR4 was then an 'orphan' receptor, in that its natural ligand was unknown; its sequence indicated that it was a G-protein-coupled receptor with seven transmembrane helices, most closely related to the receptor for the CXC chemokine IL-8. Curiously, antibodies against CXCR4 blocked the entry of T-tropic but not M-tropic strains, suggesting that their effects were the inverse of those of the β-chemokines, which block infection with M-tropic but not T-tropic strains[58] (see above). Taken together, these observations suggested that the β-chemokines inhibited infection with M-tropic strains by downregulating or blocking a second co-receptor. The β-chemokine receptor CCR5 can bind all three inhibitory chemokines[73], and a cluster of reports soon showed that it was indeed the co-receptor for M-tropic HIV-1 (refs 59, 70, 74–76). Other β-chemokine receptors (CCR2b and CCR3) can also act as co-receptors for M- and dual-tropic HIV, but they are little used by M-tropic strains[70]. Shortly afterwards, the CXC chemokine SDF-1 was shown to be the ligand for CXCR4 and to block infection with T-tropic but not M- or dual-tropic HIV-1 (refs 77, 78).

Different strains of HIV-1 thus use different chemokine receptors as co-receptors, and infection by any one strain is blocked by the ligand for the receptor in question (Fig. 3). Unlike cytokines such as TNF-α, IL-1β and IL-6, which enhance HIV replication by inducing viral gene expression[40] (see above), the β-chemokines seem to inhibit infection by blocking or downregulating the receptor they share with the virus[79] (K. Pettrone, D. Weissman and A.S.F., unpublished observations), although direct and indirect effects on signal transduction may also play a part. Further studies are thus required, particularly as the complexity of the chemokine-receptor family[73] suggests that other receptors (some perhaps not yet unidentified) may play a role in HIV entry.

Co-receptors and resistance to infection

Some individuals repeatedly exposed to HIV infection nevertheless remain uninfected, including certain commercial sex workers[80] and sexual partners of HIV-infected individuals[81]. In studies of such individuals whose PBMCs were variably resistant to infection with certain strains of HIV *in vitro*[82], cells from two individuals in particular were found to be highly resistant to infection with M-tropic virus, but readily infected with T-tropic virus. The gene for the major M-tropic receptor CCR5 was therefore sequenced, and both individuals were found to be homozygous for virtually identical 32-base-pair deletions[83], producing a truncated version of the receptor that was not expressed at the cell surface. PBMCs from these individuals did not transduce CCR5-mediated signals, although responses to other chemokines were normal. Both individuals appeared to be phenotypically fit with no host defence defects, suggesting that therapeutic strategies aimed at downregulating the receptor and/or blocking its ability to bind virus would not be deleterious (see below). Subsequent studies of HIV-1-infected cohorts have revealed no homozygotes among them[83,86].

About 20 per cent of western European caucasians are heterozygous for the defect[83,84], but it has not been found in 124 western and central Africans or in 248 Japanese, indicating that it is either absent or extremely rare in these populations[84]. The frequency of heterozygotes in a cohort of HIV-1-infected caucasians was 35 per cent less than in the general population, suggesting that heterozygosity may confer partial protection against infection[84], although this was not confirmed in another study[86]. Moreover, PBMCs from the parents of homozygous individuals replicated virus less efficiently that PBMCs from normal individuals *in vitro*[83]. Heterozygosity thus seems to provide a variable degree of protection against disease[85,86].

These findings suggest a simple model, in which the different receptors and their ligands explain the transmission and pathogenesis of T- and M-tropic strains of HIV-1, which would form an attractive basis for therapeutic and preventive strategies. But years of experience in the study of HIV suggest that even the simplest models of HIV pathogenesis can give rise to extraordinary complexities, and such models will almost certainly appear somewhat simplistic and require modification as new information becomes available.

Implications

Cellular tropism. The different receptors used by T- and M-tropic strains of HIV-1 have major implications for the basis of cellular

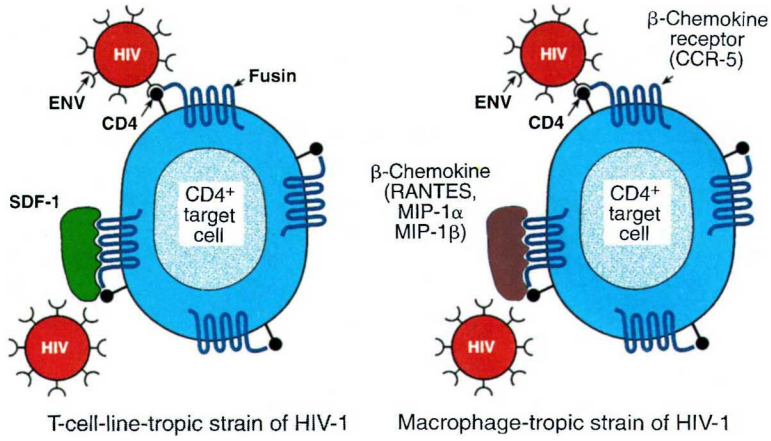

FIG. 3 Co-receptors for M- and T-tropic strains of HIV-1 on $CD4^+$ T cells. CXCR4 (fusin, LESTR) is the major co-receptor for T-tropic strains, entry of which is inhibited by its ligand SDF-1. CCR5 is the major co-receptor for M-tropic strains, and their entry is inhibited by its ligands RANTES, MIP-1α and MIP-1β. Primary T cells and monocytes express both co-receptors; the former are susceptible to both strains, but the latter can only be infected by M-tropic strains, for reasons that are not yet clear.

tropism and the mechanisms by which the virus enters target cells. Viral entry requires binding to a target cell, followed by a series of receptor-triggered conformational changes in the major viral envelope protein (Env)[59,70–72,74–76,87,88]. CD4 alone can induce conformational changes in Env, but these are insufficient for entry[89]. Several roles have thus been proposed for the newly described co-receptors, including the induction of further changes in Env by a direct or indirect association with the co-receptor, or direct binding of Env to the co-receptor, bringing the viral protein to the cell membrane to allow fusion[88]. Indeed, binding of HIV to CD4 greatly increases the efficiency of the gp120–CCR5 interaction[90,91], and there is evidence for physical association between CXCR4 and the CD4–gp120 complex in the cell membrane[92]. Chemokine-induced signalling may also depolarize or destabilize the cell membrane, assisting fusion[88], but neither G_i-protein signalling nor tyrosine kinase activity is required to inhibit M-tropic virus infection by RANTES (refs 79, 93 and K. Pettrone, D. Weissman and A.S.F., unpublished observations). Additional studies are required to delineate these events.

Viral transmission and host resistance to infection. These findings also have profound implications for the mechanisms of viral transmission and host resistance[94]. As already mentioned, M-tropic strains of HIV-1 predominate shortly after infection[64,65], and these strains are responsible for initial infection[65] even when the transmitting partner harbours both M- and T-tropic viruses[95]. The apparent resistance to infection conferred by homozygous defects in the CCR5 gene[83–86] argues strongly that intial entry of M-tropic strains into susceptible target cells is critically important for establishing HIV infection. Why this should be so is still unclear. Primary infection may be confined to cells expressing CCR5 rather than CXCR4 or other potential co-receptors, selecting M-tropic strains from among the different strains deposited at the site of exposure. Such cells may predominate at the mucosal surfaces through which the virus is sexually transmitted. Moreover, the cytokine microenvironment of the tissue in question and its state of activation may modulate susceptibility to infection by affecting receptor expression. IL-2 upregulates CCR1, CCR2 and CCR3 (ref. 96), and other immunoregulatory or proinflammatory cytokines may affect expression of both CCR5 and CXCR4 (ref. 97). The natural co-receptor ligands may also block and/or downregulate their respective receptors, as well as affecting the expression of any other co-receptors involved in HIV-1 entry. In addition, inflammation at the site of viral exposure may tip the balance between expression of the co-receptor and the corresponding ligand in favour of viral entry, explaining (at least in part) the more efficient transmission to individuals with a concomitant sexually transmitted disease producing genital inflammation[28].

Interestingly, M-tropic viruses also predominate early in the infection of individuals directly inoculated with virus (such as injecting drug users and recipients of contaminated blood products), suggesting that the aforementioned selection process may not be restricted to mucosal surfaces[98,99]. Initial infection in the reticuloendothelial system and lymphoid organs may also require cells such as monocyte/macrophages that are largely resistant to T-tropic viruses. After intravaginal inoculation of rhesus macaques with SIV, Langerhans cells beneath the mucosa are the first cells to be infected and probably initiate a spreading infection by migrating to the draining lymphoid tissue[100]. It will be interesting to know which co-receptors are present on Langerhans cells, other cells of the dendritic cell family[101] and monocytes, how their levels vary with maturation and activation, how readily these cells can be infected with various strains of HIV, and whether they can subsequently initiate infection of $CD4^+$ cells. In addition to the deletions in the CCR5 gene already discussed, other less obvious mutations in CCR5, CXCR4 and other co-receptors may be identified that affect individual susceptibility to infection. Individual susceptibility to HIV-1 is very variable, however, and can vary with time within individuals; it is probably influenced not only by specific genetic defects, but also by the relative levels of different cell types, the activation of the cellular microenvironment, the patterns of cytokine expression and secretion, and the expression of co-receptors used by different viral strains. Expression of CD4 together with a given co-receptor does not necessarily render a target cell susceptible to the corresponding virus, as shown by monocyte/macrophages that express CXCR4 (ref. 60) but are resistant to T-tropic HIV-1 (ref. 62). Moreover, infection of monocyte/macrophages by M-tropic virus is unaffected by β-chemokines[60,75,102], suggesting that alternative entry mechanisms exist.

Progression of HIV-induced disease. The discovery of this complex array of host factors also has significant implications for our understanding of the transition from M- to T-tropic strains and the progression of disease in infected individuals[67] (Fig. 4). Despite the predominance of M-tropic strains in individuals with early or stable HIV infection, some T-tropic viruses are almost invariably present[95,103]. It is still unclear why the M-tropic strains remain predominant and what triggers the eventual transition to T-tropic strains that precedes the drop in $CD4^+$ T-cell counts and the development of AIDS[66,67]. Were viral mutations alone responsible, the shift would probably occur rapidly in most infected persons, as T-tropic viruses are produced stochastically, and such viruses replicate more rapidly than M-tropic viruses *in vitro*[13]. The simplest model thus assumes that the dominance of M-tropic strains is maintained by a balance of conditions favouring the replication of M- rather than T-tropic strains, which must be disturbed by one or more events to trigger the transition. This is supported by the extended dominance of M-tropic viruses in many HIV-infected individuals, especially long-term non-progressors[104,105], which argues strongly that host factors are important in controlling the transition.

What these factors may be is a matter for speculation. As

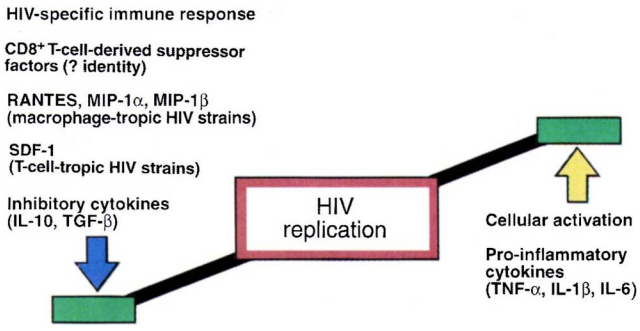

FIG. 4 Control of HIV replication and the progress of HIV-induced disease by the balance of host factors. Cellular activation and proinflammatory cytokines drive viral replication. These are counterbalanced by inhibitory factors, including both the immune system and nonspecific cytokines such as IL-10 and TGF-β, as well as co-receptor ligands such as the β-chemokines and SDF-1. Other inhibitory factors secreted by $CD8^+$ T cells remain to be identified.

lymphoid tissues are the predominant sites of viral replication and the major viral reservoir[1,8,106,107], the lymphoid microenvironment almost certainly plays a critical role. Within these tissues, low expression of CXCR4 and/or high expression of SDF-1 would inhibit replication of T-tropic strains. Interestingly, SDF-1 is produced predominantly by stromal cells rather than lymphoid cells[108], and the normal stromal architecture of lymphoid tissue may initially favour high expression of this cytokine, which would be lost as the architecture breaks down. Disruption of the lymphoid tissue architecture is characteristic of progressive HIV disease[8], and removal of a major inhibitor of T-tropic virus at the main site of viral replication could certainly initiate or exacerbate the shift to T-tropic strains. It will be important to examine SDF-1 levels in lymphoid tissue from various stages of HIV disease, as well as the effect of cytokines such as IFN-γ, TNF-α, IL-1β and IL-6 (ref. 41) on the expression of co-receptors and their ligands.

As already mentioned, active infection with *M. tuberculosis* accelerates the course of HIV disease[26,27] and the course of HIV infection in sub-Saharan Africa appears to be more fulminant than in developed countries[28–31], probably reflecting the persistent immune activation and high levels of cytokine secretion associated with chronic infection in both cases[28,32]. In addition to markedly increasing HIV gene expression[1], persistent high levels of cellular activation and proinflammatory cytokine secretion may favour the emergence of T-tropic strains by accelerating viral replication (and hence mutation), as well as modulating the relative expression of co-receptors and their ligands. The profiles of HIV-co-receptors and their ligands in PMBCs and lymphoid tissue before and after infected individuals are immunized with common recall antigens should also be of interest.

It will also be important to determine whether mutations in the gene for CXCR4 or SDF-1 exist among HIV-infected individuals, particularly long-term non-progressors, which may interfere with their ability to propagate T-tropic viruses. Homozygous defects in human SDF-1 are unlikely to be found, as mice homozygous for deletions in the gene die perinatally[109], but it is unclear whether CXCR4 is likewise essential. Similarly, the lack of disease progression and low viral burden in chimpanzees infected with HIV-1 (ref. 110), as well as the lack of disease progression despite relatively high levels of virus in certain species of monkeys[111], may well be partly explained by the profile of viral co-receptors in these species.

Therapeutic and preventive strategies. Finally, appreciation of the role of host factors in HIV-induced pathogenesis suggests new therapeutic and preventive strategies. For therapy, it will be particularly important to confirm that individuals homozygous for defects in the *CCR5* gene are phenotypically normal[83]. CD4, the primary receptor for HIV-1, is essential for immune function[112] and interfering with its function for an extended period would be problematic. With CCR5, however, therapy could be aimed at blocking or downregulating CCR5 using peptide or other ligands, or at interfering with the expression of the gene by gene therapy. For prevention, individuals could be vaccinated against co-receptor epitopes or against the domains of Env that interact with co-receptors[90,91], and it will be particularly important to map the latter precisely. The different co-receptors used by M- and T-tropic strains may also explain why vaccination with Env from T-tropic viruses induces neutralizing antibody responses against such strains, but not against primary isolates of HIV (ref. 113).

Applying these findings, however, may not be simple. The extraordinary redundancy and crossregulation of cytokines and their receptors[39] and the complexity of their interactions with HIV-1 mean that there is no guarantee that therapeutic or preventive interventions will be effective. Inhibitors of one receptor intended to block viral entry may upregulate other receptors and/or ligands, injuring a critical physiological function or even enhancing viral entry. Indeed, β-chemokines have recently been shown to enhance viral replication in monocyte/macrophages[102]. Therapeutic and preventive strategies affecting host factors, and particularly cytokines and their receptors, should be thus applied with considerable caution, beginning with animal models where possible. Despite these concerns, however, there can be no doubt that the new strategies suggested by recent advances in our understanding of host–HIV interactions have remarkable potential and should be vigorously pursued. □

Anthony S. Fauci is at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA

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