trade. It is commonly argued that industrial countries are hurt by competition from low-wage nations using "sweatshop labor"; this is just as wrong as the argument that being a low-wage country is worse than not trading at all.
5. For analysis of the effects of foreign growth on domestic welfare, see H. Johnson, *Manch. Sch. Econ. Soc. Stud.* **23**, 95 (1955). Any adverse effects would come through a worsening of the terms of trade, that is, the price of exports relative to that of imports. Excluding oil and agricultural goods, U.S. terms of trade have in fact shown a slight downward trend, but the trend is too small to have a significant negative effect on U.S. welfare [R. Lawrence, *Brookings Pap. Econ. Activity* **2:1990**, 343 (1990)].
6. Most trade in manufactured goods among industrial countries consist of "intra-industry" trade, that is, exchange of goods that seem to be produced using similar ratios of capital to labor and of skilled to unskilled workers. Thus it is difficult to explain the pattern of comparative advantage among industrial countries by differences in their resource mixes, which are in any case quite similar [H. Grubel and P. Lloyd, *Intra-Industry Trade* (Wiley, New York, 1975); E. Helpman, *J. Jpn. Int. Econ.* **1**, 62 (1987).
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# Molecular Basis of Latency in Pathogenic Human Viruses

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**Several human viruses are able to latently infect specific target cell populations in vivo. Analysis of the replication cycles of herpes simplex virus, Epstein-Barr virus, and human immunodeficiency virus suggests that the latent infections established by these human pathogens primarily result from a lack of host factors critical for the expression of viral early gene products. The subsequent activation of specific cellular transcription factors in response to extracellular stimuli can induce the expression of these viral regulatory proteins and lead to a burst of lytic viral replication. Latency in these eukaryotic viruses therefore contrasts with latency in bacteriophage, which is maintained primarily by the expression of virally encoded repressors of lytic replication.**

VIRAL INFECTIONS FREQUENTLY LEAD TO A PERIOD OF rapid viral replication that is rendered transient by an effective immune response. In many cases, this response eventually results in the complete clearance of the virus from the host animal. In some instances, however, the host immune response may be insufficiently rapid to prevent significant, even life-threatening, pathogenic effects. Historically, such acute viral infections have been the major cause of virally induced morbidity and mortality in humans. Most acutely pathogenic viruses, including the etiologic agents of smallpox, polio, measles, rubella, and mumps, can now be effectively controlled by immunization. Although some acute viral pathogens (for example, the influenza virus) remain of concern, the focus of public health interest in the developed world has increasingly been on viruses that cause long-term, chronic infections (*1*). These viruses have developed strategies to prevent elimination by the host immune response and, as a result, may also be more difficult to control by immunization (*1*).

Although viral infections have been termed latent (undetectable or asymptomatic) at the organismal level, the focus of this review is the mechanistic basis for latency at the cellular level. Here, we define latency as the reversibly nonproductive infection of a cell by a replication-competent virus. We therefore distinguish latency from irreversibly nonproductive (abortive) infections and also from persistent infections (infections that result in the continuous production of progeny virus). Mechanisms involved in the maintenance of such persistent infections, which are induced by several pathogenic human viruses, have been reviewed elsewhere (*2*).

To illustrate recent advances in the understanding of viral latency, we will focus on three human pathogens, the herpesviruses herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV), and the human immunodeficiency virus type 1 (HIV-1). In each case, we will identify candidate cellular or viral gene products involved in the three phases of viral latency. These are the initial establishment of the latent infection, the maintenance of latent infection, and, finally, the activation of productive infection. These viruses utilize latency strategies that are quite different in molecular detail. Yet each achieves the goal of maintaining viral infection for the life of the host.

## Latency in HSV-1

The classic example of viral latency is that seen with HSV-1. HSV-1, the prototype of the α or neurotropic class of herpesviruses that also includes HSV-2 and Varicella-Zoster virus (VZV), causes an initial acute infection in peripheral tissues followed by a latent

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infection of neurons (*3–5*). In these nonproliferating cells, which are sheltered from immune surveillance, the virus remains for the life of the host. More frequently for HSV-1 and HSV-2, and rarely for VZV, this dormant state is interrupted by a reactivation of lytic replication. This recrudescense is usually temporally limited and topographically constrained to peripheral tissues innervated by the latently infected neurons (*5*).

HSV-1 infects the human host through the epithelium (skin or mucous membranes). The infecting virions carry in their tegument the protein VP16 (also known as α-TIF or Vmw65), which trans-activates the α or immediate-early viral genes (*3, 6*). The VP16 protein mediates this trans-activation in association with at least two cellular factors (7) (Fig. 1). One of these, the POU domain transcription factor Oct-1, is critical for binding of VP16 to the octamer-like DNA target sequences present in the α gene promoter elements (*8*). The α gene products ICP0, ICP4, and ICP27 together trans-activate expression of the HSV-1 β (early) and γ (late) genes, which leads to virus production and cell lysis. During this initial, acute infection, HSV-1 invades the nervous system by penetrating the axon of the sensory neurons in the trigeminal nerve, and most likely the nucleocapsid is carried to the neuron body by retrograde axonal transport. In the trigeminal ganglion the virus establishes latent infection in up to 40% of neurons (*4*). The viral genome remains present at a low copy number per infected neuron in the form of unintegrated DNA circles (*3, 4, 9*).

*Establishment of HSV-1 latency.* The HSV-1 VP16 trans-activator is critical for lytic replication in vivo and enhances infectivity in tissue culture (*10*). Data indicate, however, that this viral regulatory protein is nonfunctional in neural cells (*11*). Two possible reasons for this failure have been advanced (Fig. 1). One hypothesis suggests that one of the host factors required for VP16 function is lacking in this highly differentiated cell type. Indeed, evidence indicates that Oct-1 expression is low in sensory ganglia (*12*). Alternatively, it has also been suggested that neurons may express a protein that directly inhibits VP16 function by competing for binding to octamer sequences present in the promoters of the α genes (*13*). Given the apparent lack of VP16 function in neural cells, it is perhaps not surprising that VP16 is dispensable for both establishment of, and reactivation from, latent infections in vivo (*14*).

*Maintenance of HSV-1 latency.* The only HSV-1–specific RNAs detected in latently infected neurons are ~2 kb and ~1.3 kb alternatively spliced, nonpolyadenylated, uncapped RNAs that are restricted to the cell nucleus (*15*). It has been proposed that these latency-associated transcripts (LATs) are stable introns derived from the processing of an 8.3-kb HSV-1 pre–messenger RNA (mRNA) species. The predicted mature polyadenylated mRNA (the ligated exons) is not detectable in latently infected neurons, although it is seen in lytic infection. The LAT transcription unit is antisense to, and partially overlaps with, the 3′ end of the ICP0 transcription unit, thus raising the possibility that the LATs might form an RNA duplex with the ICP0 transcript. A natural repression of the ICP0 antisense transcript was therefore invoked as the molecular basis for latency. This hypothesis was subsequently undermined by the observation that LAT$^-$ HSV-1 mutants are fully able to establish and maintain latent infections (*16, 17*). Several of these LAT$^-$ HSV mutants do, however, show a reduced level of reactivation, suggesting that the LATs play a role in facilitating this process (*17*). Although the function and the significance of the LATs remain undefined, other neurotropic herpesviruses, including HSV-2 and several animal herpesviruses, have also been shown to express LATs in latently infected neurons (*18*).

*Activation of HSV-1 replication.* HSV-1 replication can be induced by a number of apparently unrelated stimuli, including physical and emotional stress (*5*). HSV-1 can also be reactivated by damage to tissues adjacent to latently infected neurons and, particularly, by explantation of infected neurons followed by cultivation in vitro (*5*). This latter effect may in part result from deprivation of nerve growth factor 1 (NGF-1), a hormone potentially important for maintenance of the latent state in vivo (*19*).

Although the identity of the extracellular stimuli that activate productive HSV-1 replication in vivo remains unclear, reactivation probably results from a signal transduction event that either directly or indirectly induces HSV-1 α gene transcription. In fact, explantation of neurons results in the activation of several host transcription factors, including AP-1 and Oct-1 (*20*). The primary viral mediator of the switch from latency to productive infection is likely to be the HSV-1 α gene product ICP0 (Fig. 1). The ICP0 gene product is not required for establishment of latent infections and, unlike ICP4 and ICP27, is also not required for lytic infection in culture (*21*). Lack of ICP0 function is, however, associated with extremely inefficient reactivation (*21*). Unlike ICP4 and ICP27, which inhibit HSV-1 α gene expression, ICP0 trans-activates the expression of not only the HSV-1 β gene products but also the various α gene products, including itself, and is therefore capable of establishing a positive feedback loop (*3*). Direct evidence in favor of a critical role for ICP0 in the reactivation process has been obtained by use of an in vitro HSV-2 latency system (*22*). In these experiments, latently infected human fetal lung cells were found to initiate the efficient production of HSV-2 virions after superinfection with an adenovirus vector encoding the HSV-2 ICP0 gene product. In contrast, infection with vectors encoding either ICP4 or ICP0 proteins that were defective in trans-activation had no effect. In total, these observations suggest that ICP0 expression is sufficient, and probably also necessary, for the reactivation of HSV-1 replication in latently infected cells.

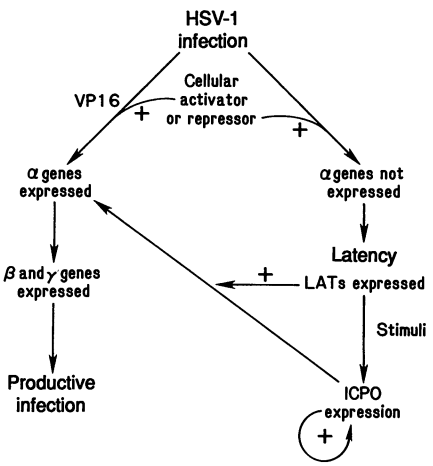


**Fig. 1.** Regulation of HSV-1 latency. Expression of the viral α gene products represents the critical first step in the lytic HSV-1 replication cycle. Generally, α gene expression is activated by the virion VP16 protein. However, if the cellular proteins required for VP16 function are lacking, or if the cell expresses an inhibitor of VP16, HSV-1 latency may be established. During latency, the HSV-1 genome expresses only the LATs. These are not required for maintenance of latency but may facilitate reactivation. Certain extracellular stimuli can induce expression of the HSV-1 α gene product ICP0. This protein positively regulates its own expression and also activates expression of the other α gene products, leading to a productive infection.

## Latency in EBV

EBV is the prototype of the γ or lymphotropic class of herpesviruses. Initial human infection with EBV results in the productive infection of epithelial cells of the nasopharynx and latent infection of peripheral B lymphocytes and can lead to a disseminated infection termed infectious mononucleosis (*23*). Whereas cells productively infected with EBV are efficiently cleared by the immune system, latently infected B cells persist for the life of the host (*23*). As with

HSV-1, it is thought that establishment of latency reflects both the lack of cellular factors critical for productive infection and the presence of cellular repressors of EBV immediate early gene expression. Nevertheless, no equivalent to the VP16 gene product of HSV-1 has been identified in EBV. The ability to establish a stable, latent EBV infection of primary human B lymphocytes in culture has provided a model system in which to probe the molecular biology of EBV latency. Much of the information reviewed below was derived from the study of such immortalized B lymphoblastoid cell lines (LCL) (*24*).

*Maintenance of EBV latency.* Latently infected LCL cells normally contain multiple episomal copies of the EBV genome. These genomes in turn express 9 out of a possible ~100 EBV gene products (Fig. 2) (*25*). The Epstein-Barr nuclear antigen (EBNA) 1 is required for the controlled replication of the EBV genome and also trans-activates at least one latency-specific EBV promoter (*26*). EBNA-2 transcriptionally trans-activates the viral latent membrane protein–1 (LMP-1) gene as well as cellular genes, such as the proto-oncogene c-*fgr* and the gene encoding the B-cell activation antigen CD23, that are believed to play a role in EBV-induced B cell growth transformation (*27*). The other EBNAs (3A, 3B, 3C, and LP) have tentatively assigned functions in latent infection; all are assumed to be transcriptional trans-activators except EBNA-LP (*24*). LMP-1 is required for the activation of human B lymphocytes (*28*), can protect lymphoblastoid cell lines from apoptosis (*29*), and is defined as a viral oncogene because of its ability to transform cultured rodent fibroblasts (*30*). LMP-2A and 2B associate with LMP-1 on the plasma membrane and may assist LMP-1 in the immortalization of lymphoid cells by interacting with a cell tyrosine kinase (*31*). Thus, characterization of the functions of these viral gene products suggests a model for EBV latency in LCLs. EBNA-1 is essential for the maintenance of the EBV genome in these proliferating cells, whereas the other EBNAs and the LMPs are required for the growth transformation and immortalization of infected B cells.

Although LCLs have been the primary model system for the study of EBV latency, data derived from the analysis of latently infected Burkitt lymphoma (BL) cell lines has raised the possibility of an alternate form of EBV latency marked by the exclusive expression of the EBNA-1 genome maintenance protein (*32, 33*). This highly restricted pattern of viral gene expression results from the use of a differentiation-specific EBNA-1 promoter element in BL cells (*33*). The observation that EBNA-2 and LMP-1 can provide targets for EBV-induced cytotoxic T lymphocytes (*34*) has led to the proposal that this more restricted pattern of latency-specific EBV gene expression might be important to the maintenance of EBV infections in vivo (*32, 33*).

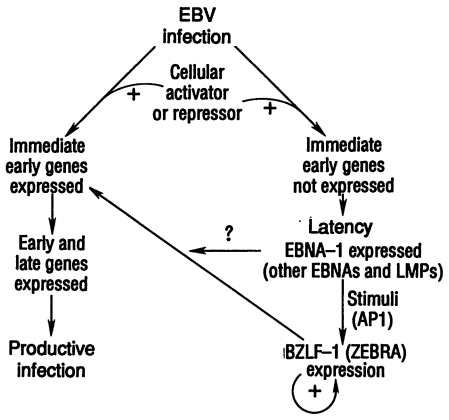


**Fig. 2.** Regulation of EBV latency. Productive infection by EBV requires the viral immediate-early gene products. These in turn are regulated by cellular factors that may activate or repress their expression. If immediate-early gene expression does not occur, then EBV may establish a latent infection. In some cell types, the latent EBV genome expresses only the genome maintenance protein EBNA-1. However, latently infected lymphocytic cell lines express not only EBNA-1 but also five other EBNA proteins and three LMPs. These other proteins are required for B cell growth transformation. Activation of EBV replication by extracellular stimuli may be mediated by the cellular transcription factor AP-1, which can induce expression of the EBV immediate-early protein ZEBRA. As in ICP0 in HSV-1, ZEBRA stimulates both its own expression as well as the expression of the other immediate-early proteins, leading to productive infection.

*Activation of EBV replication.* Although the physiological stimuli that induce EBV replication in vivo remain undefined, EBV replication can be activated in vitro by treatment of latently infected cells with any one of a number of reagents, including 12-*0* tetradecanoylphorbol-13-acetate (TPA) and antibody to immunoglobulin (*24*). These reagents are believed to act by inducing expression of ZEBRA, the gene product encoded by the EBV immediate-early gene BZLF-1 (*23*). It has been shown that expression of ZEBRA is sufficient to activate productive EBV replication (Fig. 2) (*23, 35*).

The two earliest viral transcripts detected during EBV reactivation in vitro are a ~1-kb mRNA encoding ZEBRA and a bicistronic 2.8-kb mRNA encoding ZEBRA and the BRLF1 gene product, a second EBV immediate-early gene product implicated in reactivation (*36*). It is now clear that ZEBRA trans-activates the expression of both of these transcripts, thereby creating a positive feedback loop. ZEBRA activates gene expression through cis-acting AP-1 and AP-1–like DNA sequences present in these viral promoter elements and appears to be both functionally and structurally analogous to the c-*fos* component of AP-1 (*37*). The promoter upstream of the 1-kb BZLF-1 mRNA also contains TPA-responsive AP-1 sites, thus providing an explanation for the initial activation of BZLF-1 expression by TPA. Subsequently, ZEBRA, in combination with the BRLF-1 gene product, induces expression of the other EBV immediate-early genes and thereby initiates the ordered cascade of EBV gene expression that leads eventually to virus production (*24*) (Fig. 2).

Expression of even a small amount of ZEBRA appears to be sufficient to trigger EBV reactivation. Nonetheless, spontaneous reactivation in vitro occurs at a rate of only 1 in $10^3$ to 1 in $10^6$ B cells, suggesting that activation of the BZLF-1 gene is a rare event. In contrast, in the differentiated epithelial cells of the oral cavity, ZEBRA expression appears to be efficiently activated and these cells almost invariably proceed to a productive EBV infection (*38*). How then is BZLF-1 kept silent during EBV latency in B cells? A lack of cellular activators of BZLF-1 expression, such as AP-1, is presumably important for the maintenance of latency. The demonstration of cis-acting negative regulatory sequences within the BZLF-1 promoter (*39*) has also led to the suggestion that ZEBRA expression may be actively inhibited by host factors. A more complete analysis of the cellular factors that regulate BZLF-1 expression in vivo will be critical to achieving an understanding of the regulation of EBV latency.

## Latency in HIV-1

Acute infection of humans with HIV-1 leads to a readily detectable plasma viremia and can result in infection of more than 1% of circulating $CD4^+$ T-lymphocytes (*40*). Subsequently, cells productively infected with HIV-1 are cleared by an effective host immune response, resulting in the loss of detectable free virus and in a 10- to 100-fold drop in the amount of HIV-1–infected lymphocytes. Circulating $CD4^+$ T cells, which transiently decline during acute HIV-1 infection, then return to normal levels and the patients enter a prolonged asymptomatic period (*40*). During this phase of the disease, the number of HIV-1–infected cells in the circulation gradually increases while the total $CD4^+$ T cell count declines (*41*). The consequent progressive immune dysfunction eventually compromises the ability of the host to control not only the replication of

HIV-1 but also the replication of other pathogenic viruses and microorganisms. Later stages of HIV-1–induced disease are marked by levels of $CD4^+$ T cell infection and plasma viremia comparable to those noted during the initial phase of the infection, prior to the onset of an immune response (*41*).

The persistence of HIV-1 infection in the face of a strong host immune response suggests that this virus has developed strategies to avoid immune elimination. Initial evidence in favor of latent infection came from the observation that the amount of T cells containing HIV-1 DNA in vivo was ≥10-fold higher than the amount expressing detectable viral mRNA or protein (*41, 42*). More recently, researchers have documented two distinct pathways by which HIV-1 can establish latent infections in culture and, by extension, in the infected patient (*43–45*).

*Pre-integration latency in HIV-1.* The primary target cell for HIV-1 in the peripheral blood is the $CD4^+$ T lymphocyte (*46*). However, unless activated by the presentation of appropriate antigen, these T cells remain in the $G_0$ phase of the cell cycle. In this quiescent state, lymphocytes are nonpermissive for the replication of many viruses, including HIV-1 (*45, 47*). Evidence suggests that HIV-1 virions can efficiently bind to, and fuse with, such resting $CD4^+$ lymphocytes (*45*). However, reverse transcription of the viral RNA genome and integration of the resultant double-stranded DNA proviral intermediate into the host genome appear to be inefficient (Fig. 3). The reason why these critical initial steps in the retroviral life cycle are blocked in these resting cells remains unclear, as retroviral virions appear to contain all the proteins required for both reverse transcription and proviral integration in in vitro systems. One possibility is that the nuclear import, and hence integration of proviral intermediates, may occur efficiently only during mitosis when the integrity of the nuclear membrane is compromised. But this block does not appear to exist in all resting cells, as nondividing macrophages, the second major target cells for HIV-1 replication in vivo (*46*), appear to be fully permissive for both proviral synthesis and integration (*48*).

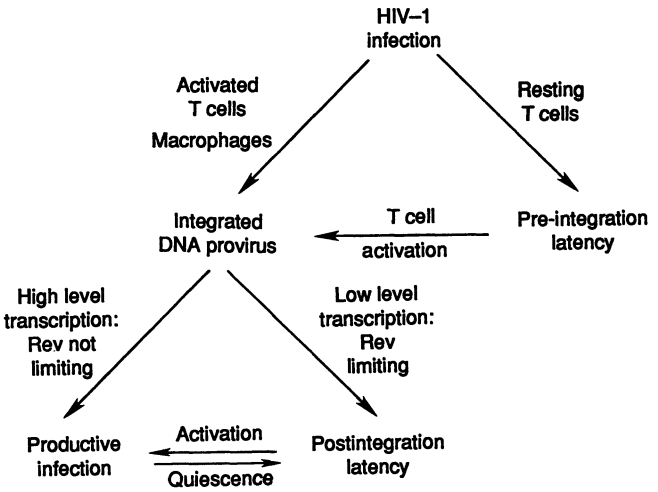


**Fig. 3.** Regulation of HIV-1 latency. Both activated T lymphocytes and nondividing macrophages are able to support the synthesis and integration of HIV-1 proviruses. In contrast, resting T cells are nonpermissive for this initial step of the HIV-1 replication cycle. However, the resultant unintegrated, proviral intermediates may persist in a viable yet transcriptionally inert form for a significant period of time. If the T cell is activated during this period, then proviral integration can ensue. In quiescent macrophages, or in T cells that have returned to a resting state, cellular factors critical for proviral transcription may not be active. The resultant inhibition of HIV-1 mRNA synthesis may lead to a amount of Rev protein expression that is insufficient to maintain production of the viral structural proteins. However, stimulation of these cells could induce these critical cellular transcription factors and activate virus production.

Results from a number of laboratories have shown that the eclipsed, extrachromosomal HIV-1 genomes observed in infected, resting T cells can be rescued by the subsequent activation of the cell, to generate integrated, transcriptionally active HIV-1 proviruses (*45*) (Fig. 3). Evidence obtained in vitro suggests that these extrachromosomal HIV-1 genomes can remain viable for several days, and possibly for several weeks, after initial infection of the resting $CD4^+$ T cell (*45*). This observation led to the hypothesis that latently infected quiescent T cells might constitute an inducible HIV-1 reservoir in infected patients. Direct evidence in favor of this hypothesis has been provided by the demonstration of high amounts of unintegrated HIV-1–proviral intermediates in T cells recovered from HIV-1–infected individuals (*49*). These unintegrated HIV-1 proviruses were predominantly associated with quiescent T cells and could be induced to integrate and initiate virus production by in vitro activation of the infected cells.

*Postintegration latency in HIV-1.* Activation of $CD4^+$ T lymphocytes triggers cellular proliferation and renders these cells fully permissive for HIV-1 replication. However, this activated state is normally transient in vivo, and cell division ceases as the cells cycle back into the resting phase as memory cells. It has been suggested that the reentry of these cells into $G_0$ might also permit establishment of a second latent form of the virus corresponding to an integrated but quiescent HIV-1 provirus (*46, 50*) (Fig. 3). Similarly, HIV-1 proviruses integrated into the genome of cells of the monocyte-macrophage lineage, which are permissive for proviral synthesis and integration even in the absence of cellular proliferation, might also be capable of maintaining a latent state. Subsequent activation of these cells by antigens, cytokines, or other stimuli might then result in reactivation of a productive HIV-1 infection (*46, 50*).

Evidence in favor of this hypothesis has been obtained from analysis of HIV-1 replication in culture. Acute in vitro infections generally result in efficient viral replication and in a marked drop in cell viability. Subsequently, however, cell viability returns to normal and HIV-1 replication declines to low or even undetectable amounts (*43*). Although this relatively nonproductive state is stable under culture conditions that minimize cell stimulation, vigorous production of HIV-1 can be induced by treatment with agents such as TPA or iododeoxyuridine and also by more physiological stimuli such as the cytokine tumor necrosis factor–α (TNF-α) (*43, 51*). HIV-1–infected cell lines derived from such "survivor cell" populations, including the promonocytic cell line U1 and the T cell line ACH-2, have therefore been advanced as useful in vitro models for the study of latent HIV-1 infection (*43, 44, 46, 51*).

HIV-1 gene expression is regulated at least at two distinct levels (*52*). Proviral transcriptional activity is determined by the interplay of a series of constitutive and inducible cellular transcription factors and, particularly, by the action of the virally encoded Tat transactivator. In addition, viral gene expression is regulated after transcription, at the level of mRNA splicing and transport, by the HIV-1 Rev protein. In principle, it would appear probable that latency after integration in HIV-1 would reflect inefficient proviral transcription. Consistent with this hypothesis, the U1 cell line expresses only low amounts of the active form of the transcription factor NF–κB (*53*). This cellular protein plays a key role in determining the amount of transcription from the HIV-1 long terminal repeat (LTR) promoter and is known to be induced by agents such as TPA and TNF-α that can reactivate latent HIV-1 proviruses (*53*). The HIV-1 Tat protein, a nuclear trans-activator that is essential for viral replication in culture, may also not be fully functional in physiologically quiescent cells (*54*).

As predicted by these considerations, TPA treatment of U1 or ACH-2 cells was observed to result in a significant increase in the

level of HIV-1 mRNA synthesis (*44, 55*). However, cell activation also resulted in a marked alteration in the pattern of viral mRNA expression. Unstimulated U1 or ACH-2 cells were found to express the multiply spliced transcripts that encode the viral regulatory proteins Tat, Rev, and Nef, but little of the unspliced HIV-1 transcript that serves as the viral genome and as the mRNA for the virion structural proteins Gag and Pol (*44, 55*). This pattern of mRNA expression is similar to that observed with HIV-1 proviruses lacking *rev* (*52*) and is identical to the pattern observed during the early phase of a productive HIV-1 replication cycle before Rev activity becomes detectable (*56*). In contrast, stimulation of these chronically infected cells led to the predominant expression of the singly spliced and, particularly, unspliced HIV-1 mRNA species that encode the viral structural proteins (*44, 55*). This shift recapitulates the change in viral gene expression from early (regulatory) to late (structural), which is observed during a productive HIV-1 replication cycle and reflects the action of the essential viral Rev trans-activator.

On the basis of these observations, it was proposed that postintegration latency in HIV-1 resulted from inefficient proviral transcription and, more directly, from a subcritical amount of Rev function (*44*) (Fig. 3). An explanation for the lack of Rev activity in these chronically infected cells was suggested by the recent observation that detectable function requires Rev protein multimerization (*57*). It is predicted that this multimerization step would become inefficient if the amount of Rev biosynthesis were to fall below a certain critical amount (*57*). It therefore appears possible that the low amount of proviral transcription observed in unstimulated U1 or ACH-2 may result in an amount of Rev protein expression that falls below this hypothetical threshold (*44*).

Although postintegration latency in HIV-1 can be shown to exist in vitro, it remains unclear whether this state can be maintained in vivo. The U1 and ACH-2 cell lines produce a low but detectable amount of HIV-1 virions and are therefore perhaps more accurately described as persistently infected (*51, 55*). Such persistently infected cells would appear unlikely to avoid immune elimination in the infected individuals. Yet, U1 and ACH-2 are proliferating cells and are therefore not truly quiescent. In vivo, infected cells might be able to maintain a fully resting state that could lead to a truly latent provirus (*50*). Recently, it was observed that HIV-1–infected T cells recovered from certain infected individuals express multiply spliced HIV-1 transcripts but little or no genomic HIV-1 mRNA (*58*). This pattern of in vivo viral gene expression is comparable to that observed in vitro with unstimulated U1 and ACH-2 cells and appears consistent with the hypothesis that integrated HIV-1 proviruses may be able to maintain a nonproductive state in vivo.

## Perspective

The ability to establish latent infections may enhance viral replication and spread in two ways. This strategy permits the virus to avoid immune elimination and to persist in a communicable form in the host animal. In addition, by predicating entry into the productive viral replication cycle on the availability of cellular transcription factors characteristic of a physiologically activated state, the virus may delay entry into the late phase of the viral replication cycle until the infected cell is able to efficiently sustain virion production. It appears likely that the ability to establish and maintain latent infections is critical to the survival and spread of HSV-1, EBV, and HIV-1.

Although research into the regulation of viral latency has only begun to approach molecular detail, it does appear that several generalizations are emerging. It seems clear that these eukaryotic viruses do not encode latency-specifying gene products analogous to the repressor proteins of bacteriophage (*59*). In contrast, it appears more generally true that viral latency both reflects and requires a block to the functional expression of the virally encoded regulatory proteins (VP16 and ICP-0 in HSV-1, ZEBRA in EBV, Tat and Rev in HIV-1) that serve as key activators of the productive replication cycle. Although this block may, in part, reflect the action of cellular repressors, it seems more likely that it is the lack of select cellular transcription factors that forms the key to the establishment and maintenance of latency. Extracellular stimuli that activate these cellular factors (for example, AP-1 in EBV and NF-κB in HIV-1) constitute the switch that induces productive viral replication. Future efforts to control the reactivation of viruses from latently infected cells by chemotherapeutic intervention will clearly have to address this intimate interconnection between host and viral gene regulation.

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