REVIEW

Molecular Interactions Between Retroviruses and Herpesviruses

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ABSTRACT. Human and animal herpesviruses are able to stimulate gene expression of various human and animal retroviruses and the activation appears to be a common theme. It is of interest why the retroviruses can be commonly activated by herpesviruses despite clear diversities in each mechanism for retrovirus gene expression. In this review, three typical examples of the interactions; human immunodeficiency virus and human herpesviruses, avian retroviruses and Marek's disease virus, and feline immunodeficiency virus and feline herpesvirus type 1 will be given to respond the above question on the basis of the comparative study of molecular interactions.—**KEY WORDS:** herpesvirus, interaction, retrovirus, transactivation.

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More than 200 years of research and development of effective vaccines, since Dr. Jenner used vaccinia virus as the first vaccine against smallpox, are able to overcome and control many viral diseases, especially acute infectious diseases [91]. On the other hand, viral diseases with no effective vaccines recently come into significant issues. Herpesviruses and retroviruses possess unique characteristics that they can establish a latent state infection in natural hosts without responding sufficient host immune defense mechanisms [71, 130]. Because of the characteristics, the development of their effective vaccines is extremely difficult in some cases. These viruses are associated with a wide variety of diseases and some of them are also known to induce neoplastic diseases in animals and humans [44, 71]. From these reasons, the viruses are considered to be one of the most important pathogens in the field of veterinary and human medicines. From approximately 20 years ago, it is suspected that interaction between herpesvirus and retrovirus can result in the synergistic induction of diseases. The first clear evidence of the interaction was demonstrated as an increased incidence of avian leukosis virus (ALV)-associated tumors in chickens by co-infection with avian herpesvirus, Marek's disease virus (MDV) [2, 33, 102]. It was also suggested that a herpesvirus infection of guinea pigs activated the endogenous retrovirus, resulting in the production of hyperplasia [56]. Further, activation and synthesis of endogenous mouse retrovirus by herpes simplex virus (HSV) *in vitro* have been reported [15, 47]. In the 1980s, the interaction was highlighted in research of human immunodeficiency virus (HIV) which is the etiologic agent of acquired immunodeficiency syndrome (AIDS) [4]. Human herpesviruses have been implicated as potential cofactors that trigger and progress an active HIV infection.

The backgrounds to support the hypothesis are as follows. (i) Herpesvirus infection is the major opportunistic infection observed in AIDS patients [49, 106, 125]. (ii) The virus is responsible for a significant proportion of the collective morbidity and mortality reported in AIDS patients [18, 53, 73, 105]. (iii) Dual infection of the same cells has been observed *in vivo* [11, 32, 94, 121]. (iv) All the human herpesviruses have been shown to be able to stimulate HIV replication and to transactivate long terminal repeat (LTR)-directed gene expression [70].

In veterinary field, it has been shown that animal herpesviruses, MDV, feline herpesvirus type 1 (FHV-1) and bovine herpesvirus type 1 (BHV-1) can transactivate LTR-directed viral gene expression of animal retroviruses, ALV [103], Rous sarcoma virus (RSV) [127], feline immunodeficiency virus (FIV) [65] and bovine immunodeficiency-like virus (BIV) [39]. Thus the activation of retroviruses by herpesviruses seems to be common phenomena. However, mechanisms for regulation of HIV gene expression are distinct from those of animal retroviruses; i.e. functional transcriptional regulatory sequences in HIV LTR are different from those in animal retrovirus LTRs (see the section of Transcriptional Regulation of Retroviruses). Therefore, it is of interest that HIV and animal retroviruses are commonly activated by herpesviruses despite clear differences in viral gene expression. This review will focus on the molecular mechanism for various interactions between herpesviruses and retroviruses with a brief prelude on transcriptional regulation of herpesviruses and that of retroviruses. To keep with the theme of this article, in the sections of "Transcriptional Regulation of Retroviruses", and "Regulatory Proteins of Herpesviruses", only brief reviews will be given. For more comprehensive overviews of gene regulation of retroviruses and herpesviruses, readers should be referred to other review articles published recently [36, 48, 83, 113, 133].

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Fig. 1. A schematic diagram of the retrovirus LTRs, indicating potential sites of interaction for DNA and RNA binding proteins, is shown. For details see section on Transcriptional Regulation of Retroviruses.

TRANSCRIPTIONAL REGULATION OF RETROVIRUSES

The retroviral genome has a LTR sequence at each end which contains regulatory elements and polyadenylation signal required for viral transcription [71]. The regulatory elements are binding sites for a number of cellular factors and whose binding activates transcription [74]. In retroviruses, LTRs play a major role in viral gene expression, tissue tropism, and pathogenesis [74]. In this section, the regulatory domains of three retrovirus LTRs (RSV, HIV and FIV) will be explained briefly. As shown in Fig. 1, a number of research groups have identified nuclear factors which recognize specific sequences in the U3 region of the RSV LTR. At 5' end of U3, there are multiple copies of the sequence, GCAAT/CA, which may be bounded by one or more of the C/EBP family (EFII, FIII, al, a4, or E2BP) [113, 114, 118]. FEII binding site possesses enhancer ability by itself [119] and mutation of this site diminished promoter activity and viral replication [115]. A second factor termed EFI, FII, E1BP or b-c binds to a sequence of inverted CCAAT motif located at -140 [113, 118] and EFI specifically recognizes another inverted CCAAT motif located at -65 [45]. Disruption of the 5' inverted CCAAT motif results in a 20-fold decrease in

promoter activity of RSV LTR and prevents EFI binding [21, 45]. To the contrary, mutation of the 3' inverted CCAAT motif has little effect on overall binding, while it dramatically reduced promoter activity [45]. An additional factor termed EFIII, recognizes two CArG motifs known as the c-fos serum response element (SRE) which mediates serum-inducible expression of c-fos through serum response factor (SRF) [13, 128]. RSV LTR is serum responsive and EFIII has shown to represent the avian homologue to the SRF, therefore, EFIII binding sites may be implicated in mediating serum response of RSV LTR [13, 14, 21].

In the U3 region of HIV LTR (Fig. 1), there are a TATA element and three tandem binding sites for the ubiquitous transcription factor, Sp-1, upstream of the transcription start site. These elements appear to be critical for basal-level of HIV gene expression [36, 61]. There are two tandem binding sites for the transcription factor, NF-κB immediately upstream of the Sp-1 binding sites. Because NF-κB is a dimer of p50/p65 *rel*-related proteins which are freed from an inhibitory complex with IκB as a result of T cell activation, the NF-κB binding sites are not only important for basal promoter activity but also for transcriptional activation of the virus in activated T lymphocytes [9, 36]. The R region is able to form a stable stem-loop structure of RNA (TAR) and this structure is required for activation by

Tat [120]. Virus-encoded tat protein acts as a potent virus-specific transcriptional activator [120]. The protein functions by recognizing the TAR and this binding results in enhancement of the ability of RNA polII complex to traverse the length of the proviral genome efficiently [120]. LBP-1 is able to bind to the R region and may act as a dominant negative inhibitor of HIV gene expression in that its binding inhibits HIV gene expression by interfering with the ability of TFIID to bind to the TATA element [36, 68]. Upstream in the U3 regions, a negative regulatory element (NRE) has been mapped [36, 111]. Some transcription factors which bind to the NRE region such as COUP-TF [96] and USF [35] may be implicated in the negative regulation.

Although there are many transcription regulatory elements in the U3 region of FIV LTR (Fig. 1), these elements are quite distinct from those of HIV, suggesting that different mechanism may be involved in regulation of FIV gene expression. AP-1, AP-4, C/EBP and ATF sites are critical for basal-level of FIV gene expression [66, 81, 124, 126] and in fact, nuclear proteins from feline T-cell line are able to bind to these sites [67, 126]. AP-1 site is required for the activation by c-Fos and for T cell activation responses

mediated by protein kinase C like NF- κ B binding site of HIV [81, 124]. ATF site is a target for c-AMP-induced responses mediated by protein kinase A [124]. C/EBP site is necessary for efficient replication of FIV in feline T-lymphocytes and is also implicated in the inhibition of FIV LTR-directed gene expression by heterologous viral regulators [67]. NRE has been mapped at 5' end of the U3 in the FIV LTR and the relevant area includes a purine-rich sequence like HIV NRE [124, 126].

REGULATORY PROTEINS OF HERPESVIRUSES

Gene expression of herpesviruses can be divided into three classes, termed immediate early (IE), early and late phases, and regulated in cascade fashion (Fig. 2) [110]. The IE gene products have a regulatory role and the functional IE gene products are important to induce expression of both early and late gene products [110, 130]. Much of the present discussion in this section will deal with alphaherpesviruses, mainly HSV-1 because their mechanisms for regulation of gene expression have been best studied among herpesviruses.

There are five IE genes in HSV-1 and these IE gene

Fig. 2. Summary of speculative models for molecular interaction between herpesvirus and retrovirus. Herpesvirus gene expression is divided into three classes and regulated in cascade fashion. The herpesvirus gene products, mainly IE proteins interact with and induce cellular proteins, and these interactions result in activation of retrovirus gene expression via transcriptional regulatory sequences in the retrovirus LTR as discussed in the text. Plus and minus signs indicate positive or negative transcriptional effects, respectively.

products possess regulatory functions [48]. Among the IE gene products, ICP4 of HSV-1 is a key essential regulator in control of HSV-1 gene expression [48, 122]. ICP4 is required for transcriptional activation of early and late genes, and repression of its own transcription [48, 122, 134]. ICP4 directly binds to particular sequences in HSV-1 promoters. These binding sites contain the consensus sequence 'ATCGTC' [29]. These are located near mRNA start sites of ICP4 and latency associated promoters [7, 90], and upstream region and 5' nontranslated leaders of some late promoters [10]. ICP4 is able to down-regulate its own and latency associated promoters by binding to the cap sites of the promoters [7, 48, 90]. In contrast to clear demonstration of mechanisms for the repression by ICP4, those for the activation of early and late promoters by ICP4 are unknown because it was found that the activation by ICP4 apparently did not require direct binding of the protein to promoters and there are no virus-specific sequences within the promoters which are strictly required for transactivation by ICP4 [24]. It is, therefore, possible to speculate that ICP4 may interact with cellular factors, especially, basal transcriptional machinery such as preinitiation complex and the RNA polymerase itself to stimulate transcription directly because only the sequences common to all the early and late promoters are TATA elements and ICP4 interacts with TATA-binding proteins [123]. In addition to transactivation of HSV-1 early and late promoters, ICP4 is able to activate certain heterologous viral promoters and cellular gene such as HIV LTR, simian virus 40 (SV40) early promoter and ubiquitin gene [26, 97, 122] and it is also capable of down-regulating FIV LTR [63].

ICP0 of HSV-1 is often termed a promiscuous transactivator. It is able to stimulate HSV-1 promoters of all three temporal classes [27] and also to activate certain heterologous promoters including SV40 early promoter and HIV LTR [26, 87]. ICP0 appears to be capable of complexing with ICP4 [48, 89] and the synergy of ICP0 with ICP4 leads to promote stronger activation than that seen with either alone [25]. In other alphaherpesviruses, ICP0 homologues have been identified and characterized. Although varicella-zoster virus (VZV) ICP0 homologue is able to transactivate VZV promoters of all the classes and heterologous promoters such as SV40 early promoter and HIV LTR [84, 85] like HSV-1 ICP0, VZV ICP0 homologue has been shown to transrepress or upregulate the function of VZV transactivators, ICP4 and ICP27 homologues, on VZV promoters, depending on the cell types [93, 100]. BHV-1 ICP0 homologue seems to act as both transactivator and transrepressor for BHV-1 promoters [136].

ICP27 of HSV-1 is an essential regulatory protein in viral replication and acts as a transactivator or transrepressor depending on the target gene [79, 109]. Positive regulation in many cases is shown to have a synergistic effect in combination with ICP4, ICP0 or both, and in some cases, ICP27 can stimulate gene expression by itself [116]. ICP27 also possesses the ability to inhibit activation by ICP0 and ICP4 [116]. Interestingly, the regulatory activity of ICP27 is independent of cis-acting elements in the promoter

sequences, but mRNA processing signals are critical for the regulation by ICP27 [16, 80, 117]. ICP27 influences the efficiency of mRNA 3'-end formation at selected poly (A) sites and reduces expression of spliced genes [16, 80, 117]. These suggest that ICP27 regulates gene expression at post-transcriptional level by affecting mRNA processing. In other alphaherpesviruses, VZV ICP27 homologue seems to act only as transactivator in that it stimulates viral early and late gene promoters, and some of heterologous promoters including HIV LTR [20, 58, 86, 101]. VZV ICP27 homologue has critical requirement for the presence of upstream elements within the heterologous promoters to mediate its transcriptional effects and the ICP27 homologue-mediated activation occurs transcriptionally [101].

In addition to the IE gene products, a virion-associated transcriptional activator, α -TIF, has a regulatory function. The α -TIF of HSV-1 is a component of tegument and plays an important role in the expression of IE genes. [8]. The α -TIF complexes with cellular transcription factors, Oct-1 and HCF, and the complex binds to a specific DNA sequence 'the TAATGARAT motif' in the promoters of the IE genes with high affinity and strongly stimulates the expression of the IE genes [40, 95, 135].

Thus, these regulatory proteins described above are thought to mainly regulate gene expression of alphaherpesviruses. The characteristics of the regulatory proteins also possess the ability to activate cellular and heterologous viral promoters. These functions of herpesviruses might be possible to interact with retroviruses and contribute to explanation of the molecular interaction between retrovirus and herpesvirus.

MOLECULAR INTERACTIONS BETWEEN RETROVIRUSES AND HERPESVIRUSES

1. MOLECULAR INTERACTIONS BETWEEN HIV AND HUMAN HERPESVIRUSES

All human herpesviruses have been shown to activate HIV gene expression [70]. For demonstration of the activation, experiments in which a chimeric construct containing the HIV LTR linked to reporter gene, chloramphenicol acetyl transferase (CAT), is tested in cultured cells are always performed and result in the enhancement of CAT expression in various types of cells infected with herpesviruses [37, 70]. The enhancement was also seen in Vero and murine cells infected with HSV-1 or simian cytomegalovirus in which the HIV LTR-CAT construct was permanently integrated into the host chromatin [87, 88].

To determine herpesvirus gene products involved in the activation of HIV gene expression, candidates were focused on IE gene products of herpesviruses because they had been previously shown to have trans-acting ability (see the section of Regulatory Proteins of Herpesviruses). In HSV-1, IE gene products of ICP4 and ICP0 are able to transactivate HIV LTR-directed gene expression, however, the effects appear to be dependent on cell types and different technical

approaches used [76, 87, 92, 97]. In HeLa cells, ICP0 or ICP4 can stimulate replication of a cotransfected proviral clone of HIV [97]. Pseudorabies virus (PRV) IE gene product, which is the HSV-1 ICP4 homologue, can stimulate HIV LTR-directed gene expression and replication [138]. ICP0 and ICP4 appear to cooperatively mediate the activation of HIV gene expression [76, 87] and synergistic cooperation between HIV *tat* and IE gene product (ICP0 or ICP4) is observed [97, 138]. Another IE gene product, ICP27 and virion protein, α -TIF, could not cause significant activation of HIV LTR [76, 87, 97]. Further investigation for the interaction of HIV with the full components of HSV gene products as might occur *in vivo* has been achieved by using HSV-1 mutant with deletion in the gene encoding IE protein, ICP0, ICP4 or ICP27. It was found that the function of ICP4, but not those of ICP0 and ICP27, is essential for augmentation of HIV replication during rapid, productive HIV infection in human CD4⁺ T lymphoid cell line (CEM cells) [1]. In contrast, during reactivation of HIV in ACH-2 cells in which HIV is expressed constitutively at a very low level [17], the functional ICP0 and ICP27, not ICP4, are critical for stimulation of HIV expression [43]. These diversity suggests that ICP27 and ICP0 may be implicated in reactivation of the quiescent provirus in latently infected cells and ICP4 may play a role in enhancement of HIV replication in the setting of productive infection.

In VZV, ICP0, ICP4 and ICP27 homologues are capable of stimulating HIV LTR-directed gene expression [58, 85, 86, 101]. In contrast to HSV-1 ICP0, VZV ICP0 homologue down-regulates the ICP4 or ICP27 homologue-mediated activation of HIV LTR significantly [93]. In human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV), the gene products involved in the activation of HIV LTR are IE proteins such as IE1 and IE2 of HCMV, and BRLF1 of EBV [5, 6, 12, 19, 41, 46, 69, 77, 98, 104, 107, 131, 137]. In human herpesvirus 6 (HHV6), two small ORFs, B701 (143-amino acids) [38] and B115 (115-amino acids) [132], and a 41-kDa nuclear protein [139] in addition to a potential IE gene product [78] show transactivation capacity of HIV LTR.

A number of mutational analyses were carried out to identify cis-acting targets in HIV LTR responding to herpesvirus transactivation. The HSV-1-, VZV- or HHV6-mediated activation of HIV LTR is greatly diminished by deletion of NF- κ B and Sp-1 binding sites in the LTR [23, 30, 38, 55, 76, 87, 97, 101, 129, 132, 139] and the NF- κ B and/or Sp-1 binding sites can confer HSV-1, VZV or HHV6 inducibility to heterologous promoters [23, 87, 101, 129]. Furthermore, HSV-1 or HHV6 infection induces the NF- κ B binding protein(s) in some cells [23, 30, 42] and the HSV-1-mediated reactivation of HIV provirus transcription in ACH-2 cells correlates with binding of the 55- and 85-kDa proteins to the NF- κ B binding site [129]. These facts suggest that HSV-1, VZV or HHV6 infection may play a role in the reactivation of HIV provirus by induction of NF- κ B binding proteins like tumor necrosis factor α (TNF α) and T cell activation signals [112]. LBP-1 binding site near the transcriptional initiation site is associated with the

transcriptional activation of HIV by HSV-1 [75, 129]. Mutation of the LBP-1 motif interferes with HSV-1-mediated HIV activation and this motif can confer HSV-1 responsiveness to heterologous promoters [75, 129]. HSV-1 infection induces an approximate 50-kDa protein, termed HLP-1, that binds to the LBP-1 binding site and its expression correlates with HSV-1-mediated reactivation of HIV provirus in ACH-2 cells [75, 129]. Interestingly, in contrast to NF- κ B, the HLP-1, which may not be identical to LBP-1 because of its difference in molecular weight, appears to be specifically induced by HSV-1 infection, but not by TNF α or mitogen [129].

It was suggested that the GGTC A palindrome in NRE of HIV LTR may be involved in HSV-1-mediated regulation of HIV LTR in U937 cells [31]. In HCMV, the LBP-1 binding site and 10-bp element between TATA element and Sp1 binding site are found to be critical for the HCMV-mediated induction of HIV LTR [5, 12, 131]. Although the regulatory elements, which are implicated in the herpesvirus-mediated activation of HIV LTR, have been reported as described above, the effects of the elements varied with cell types and mutation of any element by itself is unable to abolish the herpesvirus responsiveness [12, 30, 76, 97, 129, 131]. Furthermore, responses to herpesviruses persist despite the deletion of almost all upstream sequences from TATA element [12, 77, 87, 97, 104, 131]. These facts suggest that basal transcriptional machinery such as TATA element-binding factors may be partially involved in herpesvirus-mediated activation of HIV LTR. Indeed, HSV-1 ICP4 and HCMV IE2, which can act to transactivate HIV LTR, have been shown to directly interact TATA element-binding factors [46, 123]. Finally reciprocal interactions have been shown in HCMV and HHV6. HIV *tat* enhances HCMV gene expression and replication [51, 52], while it inhibits HHV6 replication [72].

2. MOLECULAR INTERACTIONS BETWEEN ANIMAL RETROVIRUSES AND HERPESVIRUSES

The only clear evidence for interaction between herpesvirus and retrovirus *in vivo* was demonstrated in infection with MDV and avian retroviruses (RSV and ALV). Development of lymphoid leukosis (LL) induced by ALV was significantly augmented in chickens by MDV infection [2, 33, 102]. Particles of herpesvirus and type-C retrovirus coexisted in the same cells of chickens co-infected with MDV and ALV [50]. MDV groups into three serotypes based on serology and pathogenesis, pathogenic strain (MDV1), nononcogenic strain (MDV2) and the related nononcogenic herpesvirus of turkeys (HVT) [99]. The augmentation of ALV-induced diseases by MDV *in vivo* varied with the MDV serotypes. MDV2 strongly augments LL induced by ALV, but HVT does not [2]. The augmentation of LL by MDV1 was intermediate in effect [2]. Like HIV and human herpesviruses, RSV LTR-directed gene expression and ALV replication are activated by MDV *in vitro* [103, 127]. The ability to transactivate RSV LTR by MDV is dependent on the serotypes and MDV2

stimulates RSV gene expression more efficiently than MDV1 and HVT do. These *in vitro* results appear to be linked with the different degree of the augmentation of ALV-mediated diseases by MDV serotypes observed *in vivo* [2, 127], suggesting that the different effects may be due to the divergence in the gene products of the MDV serotypes such as IE proteins. Although molecular mechanism for the activation of RSV LTR by MDV remains to be elucidated, MDV ICP4 homologue and a sequence between -140 and -120 which is critical for basal promoter activity of the RSV LTR and to which a nuclear factor, EFl, binds (Fig. 1) appear to be implicated in the activation [3]. It was also shown that MDV infection induces a nuclear protein(s) which binds to the sequence between -140 and -120 [3]. In the case of MDV and ALV, reciprocal enhancement can not be observed and ALV replication inhibits MDV replication [34]. Avian retroviruses including ALV and reticuloendotheliosis virus can readily integrate into herpesvirus genome in co-infected cells [59, 60] and this insertion may affect the replication ability of MDV *in vitro* and also pathogenicity of the herpesvirus *in vivo*.

Animal lentivirus, FIV, shares some characteristics with HIV such as cell tropisms for T-lymphocytes and macrophage *in vivo* and association with immunodeficiency-like diseases in cats [82]. To the contrary, genomic organization of FIV are simpler than that of HIV and functional transcriptional regulatory elements in the FIV LTR are different from those in HIV LTR [83]. Feline herpesvirus, FHV-1, is able to replicate in feline T-lymphocytes [54], and dual infection of feline T-Lymphocytes with FIV and FHV-1 has been demonstrated *in vitro* [65]. Like other retroviruses, FIV LTR-directed gene expression can be stimulated by FHV-1 [65] and the stimulation was observed in feline renal cells infected with FHV-1 in which the FIV LTR was permanently integrated into the host genome [57]. Precise region which responds to the activation by FHV-1 is largely unknown, however, the sequence between -63 and -23 which contains ATF site and TATA element (Fig. 1) appears to be involved in the FHV-1 stimulation [66]. A low but consistent transactivation by FHV-1 was still observed after deletion of almost all upstream sequences from TATA element like HIV and human herpesviruses [66].

It is noteworthy that ICP4 homologues of other alphaherpesviruses including PRV, HSV-1 and equine herpesvirus type 1 significantly down-regulate FIV gene expression and replication in feline cells [63]. Because it is thought that activation of retroviruses by herpesvirus IE proteins appears to be common theme [28, 70], the inhibition of FIV gene expression by the ICP4 homologues is unique. Mutation of the C/EBP site in FIV LTR interferes with PRV ICP4-mediated FIV inhibition and this site can confer the ICP4 homologue responsiveness to a heterologous promoter [67], indicating that the C/EBP site is involved in the ICP4 homologue-mediated FIV down-regulation. In FHV-1, only IE gene product, ICP4 homologue, has been identified and characterized [62]. However, the FHV-1 ICP4 homologue could neither transactivate nor down-

regulate FIV LTR-directed gene expression in the feline cells in which FIV LTR is stimulated by FHV-1 infection and is down-regulated by other alphaherpesvirus ICP4 homologues [62, 63, 65]. Interestingly, the FHV-1 ICP4 homologue could transactivate FIV gene expression in human colon carcinoma cells (SW480 cells) [62] and it could up-regulate FIV LTR-directed gene expression after the site-specific deletion of the C/EBP site in the feline cells [64]. These results suggest that the FHV-1 ICP4 homologue possesses both abilities to transactivate and transrepress FIV LTR.

The FIV/FHV-1 system is considered to be an ideal model to examine the interaction between lentivirus and herpesvirus since cats are the smallest animal which can be naturally infected with lentivirus and *in vitro* results can be readily testable *in vivo*. The interaction between FIV and FHV-1 was investigated using specific pathogen free (SPF) cats *in vivo*. When SPF cats which had been infected with FIV 18 month before and were at a stage of an asymptomatic carrier phase were exposed to FHV-1, symptom of feline viral rhinotracheitis caused by FHV-1 in FIV-infected cats became severer than that of non-FIV infected cats, however, manifestation of immunodeficiency-like diseases could not be observed during the 2 month after FHV-1 infection [108]. It is considered that cats infected latently with FHV-1 sometime recrudesces and at each time FHV-1 may stimulate the FIV LTR. The repeated stimulation during several years may result in the conversion from a FIV latency to a clinical manifestation of the immunodeficiency-like diseases and also in enhancement of the diseases. Therefore, 2 months incubation period after FHV-1 infection may not be long enough to show clear differences in the manifestation of the immunodeficiency-like diseases. In fact, English [22] recently reported that random-source cats which latently infected with FHV-1 frequently developed clinical diseases typical of feline AIDS, recurrent upper respiratory disease, 18–24 months after FIV infection and high titers of FHV-1 were isolated from these cats. These data suggest that FHV-1 may play a role in the development of feline AIDS *in vivo*.

In another animal immunodeficiency virus, BIV LTR-directed gene expression and replication are stimulated by BHV-1 [39]. The activation could be abolished by deletion of 5' end of the U3 region at position -429 to -330 which contains a potential NF- κ B binding site and BHV-1 infection induces a nuclear factor which binds to both the potential BIV and HIV NF- κ B binding sites [39]. These facts suggest that mechanisms for the BHV-1-mediated BIV activation may be similar to that for the activation of HIV gene expression by HSV-1 or HHV6.

CONCLUSIVE REMARKS

A variety of human and animal retroviruses can be commonly activated by human and animal herpesviruses in spite of the divergence in each mechanism for retrovirus gene regulation. The common phenomena for the activation by herpesviruses might be attributable to mechanisms that

herpesvirus gene products, mainly IE proteins, interact with and affect the basal transcriptional machinery during herpesvirus infection, and this effect results in the retrovirus activation. Moreover, herpesvirus infection might be able to induce a number of transcriptional factors and some of them which are capable of interacting with each retrovirus LTR may also be involved in the activation of retrovirus in concert with the effect of herpesvirus interaction with the basal transcriptional machinery (Fig. 2).

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REFERENCES

- Albrecht, M. A., DeLuca, N. A., Byrn, R. A., Schaffer, P. A., and Hammer, S. M. 1989. The herpes simplex virus immediate-early protein, ICP4, is required to potentiate replication of human immunodeficiency virus in CD4⁺ lymphocytes. *J. Virol.* 63: 1861–1868.
- Bacon, L. D., Witter, R. L., and Fadly, A. M. 1989. Augmentation of retrovirus-induced lymphoid leukosis by Marek's disease herpesviruses in white leghorn chickens. *J. Virol.* 63: 504–512.
- Banders, U. T., and Coussens, P. M. 1994. Interactions between Marek's disease virus encoded or induced factors and the Rous sarcoma virus long terminal repeat promoter. *Virology* 199: 1–10.
- Barre-Sinoussi, F., Chermann, J. C., Rey, R., Nugeyre, M. T., Chamaret, S., Gruest, J., Dauget, C., Axler-Blin, C., Veziner-Brun, F., Rouzioux, C., Rosenbaum, W., and Montagnier, L. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* 220: 868–871.
- Barry, P. A., Pratt-Lowe, E., Peterlin, B. M., and Luciw, P. A. 1990. Cytomegalovirus activates transcription directed by the long terminal repeat of human immunodeficiency virus type 1. *J. Virol.* 64: 2932–2940.
- Barry, P. A., Pratt-Lowe, E., Unger, R. E., and Luciw, P. A. 1991. Cellular factors regulate transactivation of human immunodeficiency virus type 1. *J. Virol.* 65: 1392–1399.
- Batchelor, A. H. and O'Hare, P. 1990. Regulation and cell-type-specific activity of a promoter located upstream of the latency-associated transcript of the herpes simplex virus type 1. *J. Virol.* 64: 3269–3279.
- Batterson, W. and Roizman, B. 1983. Characterization of the herpes simplex virion-associated factor responsible for induction of α genes. *J. Virol.* 46: 371–377.
- Bauerle, P. and Baltimore, D. 1988. I κ B: a specific inhibitor of the NF κ B transcription factor. *Science* 242: 540–546.
- Beard, P., Faber, S., Wilcox, K. W., and Pizer, L. I. 1986. Herpes simplex virus immediate early infected-cell polypeptide 4 binds to DNA and promotes transcription. *Proc. Natl. Acad. Sci.* 83: 4016–4020.
- Belec, L., Gray, F., Mikol, J., Mikol, J., Scaravilli, F., Mhiri, C., Sobel, A., and Poirier, J. 1990. Cytomegalovirus encephalomyeloradiculitis and human immunodeficiency virus encephalitis: Presence of HIV and CMV co-infected multinucleated giant cells. *Acta Neuropathol.* 81: 99–104.
- Biegalka, B. J. and Geballe, A. P. 1991. Sequence requirements of activation of the HIV-1 LTR by human cytomegalovirus. *Virology* 183: 381–385.
- Boulden, A. and Sealy, L. 1990. Identification of a third protein factor which binds to the Rous sarcoma virus LTR enhancer: possible homology with the serum response factor. *Virology* 174: 204–216.
- Boulden, A. M. and Sealy, L. J. 1992. Maximal serum stimulation of the c-fos serum response element requires both the serum response factor and a novel binding factor, SRE-binding protein. *Mol. Cell. Biol.* 12: 4769–4783.
- Boyd, A. L., Enquist, L., Vande Woude, G. F., and Hampar, B. 1980. Activation of mouse retrovirus by herpes simplex virus type 1 cloned DNA fragments. *Virology* 103: 228–231.
- Chapman, C. J., Harris, J. D., Haedwicke, M. A., Sandri-Goldin, R. M., Collins, M. K. L., and Latchman, D. S. 1992. Promoter independent activation of heterologous gene expression by the herpes simplex virus immediate-early protein ICP27. *Virology* 186: 573–578.
- Clouse, K. A., Powell, D., Washington, I., Poli, G., Strebel, K., Farrar, W., Barstad, P., Kovacs, J., Fauci, A. S., and Folks, T. M. 1989. Monokine regulation of human immunodeficiency virus-1 expression in a chronically infected human T-cell line. *J. Immunol.* 142: 431–438.
- Colebunders, R., Mann, J. M., Francis, H., Bila, K., Izaley, L., Ilwaja, M., Kakonde, N., Quinn, T., Curran, T., and Piot, A. 1988. Herpes zoster in African patients: a clinical predictor of human immunodeficiency virus infection. *J. Infect. Dis.* 157: 314–318.
- Davis, M. G., Kenney, S. C., Kamine, J., Pagano, J. S., and Huang, E. S. 1987. Immediate-early gene region of human cytomegalovirus trans-activates the promoter of human immunodeficiency virus. *Proc. Natl. Acad. Sci. U.S.A.* 84: 8642–8646.
- Defechereux, P., Melen, L., Baudoux, L., Merville-louis, M.-P., Rentier, B., and Piette, J. 1993. Characterization of the regulatory functions of varicella-zoster virus open reading frame 4 gene product. *J. Virol.* 67: 4379–4385.
- Dutta, A., Stoeckle, M. Y., and Hanafusa, H. 1990. Serum and v-src increase the level of a CCAAT-binding factor required for transcription from a retroviral long terminal repeat. *Genes Dev.* 4: 243–254.
- English, R. V., Nelson, P., Johnson, C. M., Nasisse, M., Tompkins, W. A., and Tompkins, M. B. 1994. Development of clinical disease in cats experimentally infected with feline immunodeficiency virus. *J. Infect. Dis.* 170: 543–552.
- Ensoli, B., Lusso, P., Schachter, F., Josephs, S. F., Rappaport, J., Negro, F., Gallo, R. C., and Wong-Staal, F. 1989. Human herpes virus-6 increases HIV-1 expression in co-infected T cells via nuclear factors binding to the HIV-1 enhancer. *EMBO J* 8: 3019–3027.
- Everett, R. D. 1984. A detailed analysis of an HSV-1 early promoter: sequences involved in transactivation by viral immediate-early gene products are not early gene specific. *Nucleic Acids Res.* 12: 3037–3056.
- Everett, R. D. 1984. Transactivation of transcription by herpes virus products: requirement for two HSV-1 immediate-early polypeptides for maximum activity. *EMBO J* 3: 3135–3141.
- Everett, R. D. 1988. Promoter sequence and cell type can dramatically affect the efficiency of transcriptional activation

- induced by herpes simplex virus type 1 and its immediate-early gene products Vmw175 and Vmw110. *J. Mol. Biol.* 203: 739–751.
27. Everett, R. D., Preston, C. M., and Stow, N. D. 1991. Functional and genetic analysis of the role of Vmw100 in herpes simplex virus replication. pp. 49–76. *In: Herpesvirus Transcription and Its Regulation* (Wagner, E. K. ed.), CRC, Boston.
 28. Evermann, J. F., Derse, D., and Dorn, P. L. 1991. Interactions between herpesviruses and retroviruses: implications in the initiation of disease. *Microbial. Pathogenesis* 10: 1–9.
 29. Faber, S. W. and Wilcox, K. W. 1986. Association of the herpes simplex virus regulatory protein ICP4 with specific nucleotide sequences in DNA. *Nucleic Acids Res.* 14: 6067–6083.
 30. Feng, C.-P., Kulka, M., and Aurelian, L. 1993. NF- κ B binding proteins induced by HSV-1 infection of U937 cells are not involved in activation of human immunodeficiency virus. *Virology* 192: 491–500.
 31. Feng, C.-P., Kulka, M., and Aurelian, L. 1993. The GGTCA palindrome and cognate cellular factors in trans-regulation of human immunodeficiency virus long terminal repeat by herpes simplex virus. *J. Gen. Virol.* 74: 715–723.
 32. Finkle, C., Tapper, M. A., Knox, K. K., and Carrigan, D. R. 1991. Coinfection of cells with human immunodeficiency virus and cytomegalovirus in lung tissues of patients with AIDS. *J. Acquired Immune Defic. Syndr.* 4: 735–737.
 33. Frankel, J. W. 1976. Experimental models for DNA-RNA viral interaction: A brief review. *Cancer Res.* 36: 670–673.
 34. Frankel, J. W. and Groupe, V. 1971. Interactions between Marek's disease herpesvirus and avian leukosis virus in tissue culture. *Nature New Biol.* 234: 125–126.
 35. Garcia, J. A., Gutierrez, M. I., Menzo, S., Fagagna, F. D. A. D., and Falaschi, A. 1992. A human binding site for transcription factor USF/MLTF mimics the negative regulatory element of human immunodeficiency virus type 1. *Virology* 186: 133–147.
 36. Gaynor, R. 1992. Cellular transcription factors involved in the regulation of HIV-1 gene expression. *AIDS* 6: 347–363.
 37. Gendelman, H. E., Phelps, W., Feigenbaum, L., Ostrove, J. M., Adachi, A., Howley, P. M., Khoury, G., Ginsberg, H. S., and Martin, M. A. 1986. Trans-activation of the human immunodeficiency virus long terminal repeat sequence by DNA viruses. *Proc. Natl. Acad. Sci. U.S.A.* 83: 9759–9763.
 38. Geng, Y., Chandran, B., Josephs, S. F., and Wood, C. 1992. Identification and characterization of a human herpesvirus 6 gene segment that transactivates the human immunodeficiency virus type 1 promoter. *J. Virol.* 66: 1564–1570.
 39. Geng, Y., Kashanchi, F., and Wood, C. 1992. Activation of bovine immunodeficiency-like virus expression by bovine herpesvirus type 1. *Virology* 187: 832–836.
 40. Gerster, T. and Roeder, R. G. 1988. A herpesvirus trans-acting protein interacts with transcription factor OTF-1 and other cellular proteins. *Proc. Natl. Acad. Sci.* 85: 6347–6351.
 41. Ghazal, P., Young, J., Giulietti, E., DeMattei, C., Garcia, J., Gaynor, R., Stenberg, R. M., and Nelson, J. A. 1991. A discrete cis element in the human immunodeficiency virus long terminal repeat mediates synergistic trans activation by cytomegalovirus immediate-early proteins. *J. Virol.* 65: 6735–6742.
 42. Gimbel, J. M., Duh, E., Ostrove, J. M., Gendelman, H. E., Max, E. E., and Rabson, A. B. 1988. Activation of the human immunodeficiency virus long terminal repeat by herpes simplex virus type 1 is associated with induction of a nuclear factor that binds to the NF- κ B/core enhancer sequence. *J. Virol.* 62: 4104–4112.
 43. Golden, M. P., Kim, S., Hammer, S. M., Ladd, E. A., Schaffer, P. A., DeLuca, N., and Albrecht, M. A. 1992. Activation of human immunodeficiency virus by herpes simplex virus. *J. Infect. Dis.* 166: 494–499.
 44. Green, M. 1985. Transformation and oncogenesis: DNA viruses. pp. 183–234. *In: Virology* (Fields, B. N. ed.), Raven, New York.
 45. Greuel, B., Sealy, L., and Majors, J. E. 1990. Transcriptional activity of the Rous sarcoma virus long terminal repeat correlates with binding of a factor to an upstream CCAAT box *in vitro*. *Virology* 177: 33–43.
 46. Hagemeyer, C., Walker, S., Caswell, R., Kouzarides, T., and Sinclair, J. 1992. The human cytomegalovirus 80-kilodalton but not the 72-kilodalton immediate-early protein transactivates heterologous promoters in a TATA box-dependent mechanism and interacts directly with TFIID. *J. Virol.* 66: 4452–4456.
 47. Hampar, B., Aaronson, S. A., Derge, J. G., Chakrabarty, M., Showalter, S. D., and Dunn, C. Y. 1976. Activation of an endogenous mouse type C virus by ultraviolet-irradiated herpes simplex virus type 1 and 2. *Proc. Natl. Acad. Sci. U.S.A.* 73: 646–650.
 48. Hayward, G. S. 1993. Immediate-early gene regulation in herpes simplex virus. *Semin. Virol.* 4: 15–23.
 49. Hirsch, M. S. and Felsenstein, D. 1984. Cytomegalovirus-induced immunosuppression. *Ann. New York Acad. Sci.* 437: 8–15.
 50. Hirumi, H., Frankel, J. W., Prickett, C. O., and Maramorosch, K. 1974. Coexistence of particles resembling herpesvirus and type-C virus in feather follicle epithelium of chicken. *J. Natl. Cancer Inst.* 52: 303–306.
 51. Ho, W., Ayyavoo, V., Alagarsamy, S., Stinski, M. F., Plotkin, S. A., and Gonczol, E. 1991. Human immunodeficiency virus type 1 tat gene enhances human cytomegalovirus gene expression and viral replication. *AIDS Res. Hum. Retroviruses* 7: 689–695.
 52. Ho, W. Z., Harouse, J. M., Rando, R. F., Gonczol, E., Srinivasan, A., and Plotkin, S. A. 1990. Reciprocal enhancement of gene expression and viral replication between human cytomegalovirus and human immunodeficiency virus type 1. *J. Gen. Virol.* 71: 97–103.
 53. Holmberg, S. D., Stuart, J. A., Gerber, A. R., Byers, R. H., Le, F. K., O'Malley, P. M., and Nahmias, A. J. 1988. Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA* 259: 1048–1050.
 54. Horimoto, T., Kawaguchi, Y., Limcumpao, J. A., Miyazawa, T., Takahashi, E., and Mikami, T. 1991. Replication of feline herpesvirus type 1 in feline T-lymphoblastoid cells. *J. Vet. Med. Sci.* 53: 503–505.
 55. Horvat, R. T., Wood, C., Josephs, S. F., and Balachandran, N. 1991. Transactivation of the human immunodeficiency virus promoter by human herpesvirus 6 (HHV6) strains GS and Z-29 in primary human T lymphocytes and identification of transacting HHV-6 (GS) gene fragments. *J. Virol.* 65: 2895–2902.
 56. Hsiung, G. D. and McTighe, A. H. 1976. An animal model for DNA-RNA virus interaction based upon virological and histological findings. *Cancer Res.* 36: 674–677.
 57. Ikeda, Y., Kawaguchi, Y., Tomonaga, K., Inoshima, Y., Miyazawa, T., and Mikami, T. 1995. Regulatory properties of the integrated long terminal repeat of the feline immuno-

- deficiency virus. (Submitted for publication).
58. Inchauspe, G. and Ostrove, J. M. 1989. Differential regulation by varicellazoster virus (VZV) and herpes simplex virus type-1 trans-activating genes. *Virology* 173: 710-714.
 59. Isfort, R., Jones, D., Witter, R., and Kung, H.-J. 1992. Retrovirus insertion into herpesvirus *in vitro* and *in vivo*. *Proc. Natl. Acad. Sci.* 89: 991-995.
 60. Isfort, R., Witter, R., and Kung, H.-J. 1992. Retrovirus insertion into herpesviruses. *Trend Microbiol.* 2: 174-177.
 61. Jones, K., Kadonaga, J., Luciw, P., and Tjian, R. 1986. Activation of the AIDS retrovirus promoter by the cellular transcription factor Sp1. *Science* 232: 755-759.
 62. Kawaguchi, Y., Maeda, K., Miyazawa, T., Ono, M., Kai, C., and Mikami, T. 1994. Nucleotide sequence and characterization of the feline herpesvirus type 1 immediate early gene. *Virology* 204: 430-435.
 63. Kawaguchi, Y., Maeda, K., Miyazawa, T., Ono, M., Tsubota, K., Tomonaga, K., and Mikami, T. 1994. Inhibition of feline immunodeficiency virus gene expression and replication by alphaherpesvirus ICP4 homologues. *J. Gen. Virol.* 75: 2783-2787.
 64. Kawaguchi, Y., Maeda, K., Pecoraro, M. R., Inoshima, Y., Jang, H.-K., Kohmoto, M., Iwatsuki, K., Ikeda, Y., Shimojima, M., Tohya, Y., Kai, C., and Mikami, T. 1995. The feline herpesvirus type 1 ICP4 down-regulates feline immunodeficiency virus long terminal repeat (LTR)-directed gene expression via the C/EBP site in the LTR. *J. Vet. Med. Sci.* (In press).
 65. Kawaguchi, Y., Miyazawa, T., Horimoto, T., Itagaki, S., Fukasawa, M., Takahashi, E., and Mikami, T. 1991. Activation of feline immunodeficiency virus long terminal repeat by feline herpesvirus type 1. *Virology* 184: 449-454.
 66. Kawaguchi, Y., Norimine, J., Miyazawa, T., Kai, C., and Mikami, T. 1992. Sequences within the feline immunodeficiency virus long terminal repeat that regulate gene expression and respond to activation by feline herpesvirus type 1. *Virology* 190: 465-468.
 67. Kawaguchi, Y., Tomonaga, K., Maeda, K., Ono, M., Miyazawa, T., Kohmoto, M., Tohya, Y., and Mikami, T. 1995. The C/EBP site in the feline immunodeficiency virus (FIV) long terminal repeat is necessary for its efficient replication and is also involved in the inhibition of FIV LTR-directed gene expression by pseudorabies virus ICP4. *Virology* 208: 492-499.
 68. Kato, H., Horikoshi, M., and Roeder, R. G. 1991. Repression of HIV-1 transcription by a cellular protein. *Science* 251: 1476-1479.
 69. Kenney, S., Kamine, J., Markovitz, D., Fenrick, R., and Pagano, J. 1988. An Epstein-Barr virus immediate-early gene product trans-activates gene expression from the human immunodeficiency virus long terminal repeat. *Proc. Natl. Acad. Sci. U.S.A.* 85: 1652-1656.
 70. Laurence, J. 1990. Molecular interactions among herpesviruses and human immunodeficiency viruses. *J. Infect. Dis.* 162: 338-346.
 71. Lowy, D. R. 1985. Transformation and oncogenesis: Retroviruses. pp. 235-263. In: *Virology* (Fields, B. N. ed.), Raven, New York.
 72. Luca, D. D., Secchiero, P., Bovenzi, P., Rotola, A., Caputo, A., Monini, P., and Cassai, E. 1991. Reciprocal in vitro interactions between human herpesvirus-6 and HIV-1 tat. *Acquir. Immunol. Defi. Syndr.* 5: 1095-1098.
 73. Macher, A. M., Reichert, C. M., Straus, S. E., Longo, D. L., Parrillo, J., Lane, H. C., Fauci, A. S., Rook, A. H., Manischewitz, J. F., and Quinnan G. V. Jr. 1983. Death in the AIDS patient. Role of cytomegalovirus. *New Engl. J. Med.* 309: 1454.
 74. Majors, J. 1990. The structure and function of retroviral long terminal repeats. *Curr. Top. Microbiol. Immunol.* 157: 49-92.
 75. Margolis, D. M., Ostrove, J. M., and Straus, S. E., 1993. HSV-1 activation of HIV-1 transcription is augmented by a cellular protein that binds near the initiator element. *Virology* 192: 370-374.
 76. Margolis, D. M., Rabson, A. B., Straus, S. E., and Ostrove, J. M. 1992. Transactivation of the HIV-1 LTR by HSV-1 immediate-early genes. *Virology* 186: 788-791.
 77. Markovitz, D. M., Kenne, S., Kamine, J., Smith, M. S., Davis, M., Huang, E.-S., Rosen, C., and Pagano, J. 1989. Disparate effects of two herpesviruses immediate-early gene trans-activators on HIV-1 LTR. *Virology* 173: 750-754.
 78. Martin, M. D., Nicholas, J., Thomson, B. J., Newman, C., and Honess, R. 1991. Identification of a transactivating function mapping to the putative immediate-early locus of human herpesvirus 6. *J. Virol.* 65: 5381-5390.
 79. McCarthy, A. M., McMahan, L., and Schaffer, P. A. 1989. Herpes simplex virus type 1 ICP27 deletion mutants exhibit altered patterns of transcription and are DNA deficient. *J. Virol.* 63: 18-27.
 80. McLauchlan, J., Phelan, A., Loney, C., Sandri-Goldin, R. M., and Clements, J. B. 1992. Herpes simplex virus IE63 acts at the posttranscriptional level to stimulate viral mRNA 3' processing. *J. Virol.* 66: 6939-6945.
 81. Miyazawa, T., Kohmoto, M., Kawaguchi, Y., Tomonaga, K., Toyosaki, T., Ikuta, K., Adachi, A., and Mikami, T. 1993. The AP-1 binding site in the feline immunodeficiency virus long terminal repeat is not required for virus replication in feline T lymphocytes. *J. Gen. Virol.* 74: 1573-1580.
 82. Miyazawa, T. and Mikami, T. 1993. Biological nature of feline immunodeficiency virus. *J. Vet. Med. Sci.* 55: 519-526.
 83. Miyazawa, T., Tomonaga, K., Kawaguchi, Y., and Mikami, T. 1994. The genome of feline immunodeficiency virus. *Arch. Virol.* 134: 221-234.
 84. Moriuchi, H., Moriuchi, M., Smith, H. A., Straus, S. E., and Cohen, J. I. 1992. Varicella-zoster virus open reading frame 61 protein is functionally homologous to herpes simplex virus type 1 ICP0. *J. Virol.* 66: 7303-7308.
 85. Moriuchi, H., Moriuchi, M., Straus, S. E., and Cohen, J. I. 1993. Varicellazoster virus (VZV) open reading frame 61 protein transactivates VZV gene promoters and enhances the infectivity of VZV DNA. *J. Virol.* 67: 4290-4295.
 86. Moriuchi, H., Moriuchi, M., Straus, S. E., and Cohen, J. I. 1994. Varicellazoster virus (VZV) open reading frame 4 protein is functionally distinct from and does not complement its herpes simplex virus type 1 homolog ICP27. *J. Virol.* 68: 1987-1992.
 87. Mosca, J. D., Bednarik, D. P., Raj, N. B. K., Rosen, C. A., Sodroski, J. G., Haseltine, W. A., Hayward, G. S., and Pitha, P. M. 1987. Activation of human immunodeficiency virus by herpesvirus infection: identification of a region within the long terminal repeat that responds to a trans-acting factor encoded by herpes simplex virus type 1. *Proc. Natl. Acad. Sci. U.S.A.* 84:7408-7412.
 88. Mosca, J. D., Bednarik, D. P., Raj, N. B. K., Rosen, C. A., Sodroski, J. G., Haseltine, W. A., and Pitha, P. M. 1987.

- Herpes simplex virus type-1 can reactivate transcription of latent human immunodeficiency virus. *Nature (Lond.)* 325: 67-70.
89. Mullen, M.-A., Ciufo, D. M., and Hayward, G. S. 1994. Mapping of intracellular localization domains and evidence for colocalization interactions between the IE110 and IE175 nuclear transactivator proteins of herpes simplex virus. *J. Virol.* 68: 3250-3266.
 90. Muller, M. T. 1987. Binding of the herpes simplex virus immediate-early gene product ICP4 to its own transcription start site. *J. Virol.* 61: 858-865.
 91. Murphy, B. R. and Chanock, R. M. 1985. Immunization against viruses. pp. 349-370. *In: Virology* (Fields, B. N. eds.), Raven, New York.
 92. Nabel, G. J., Rice, S. A., Knipe, D. M., and Baltimore, D. 1988. Alternative mechanisms for activation of human immunodeficiency virus enhancer in T cells. *Science* 239: 1299-1302.
 93. Nagpal, S. and Ostrove, J. M. 1991. Characterization of a potent varicella-zoster virus-encoded trans-repressor. *J. Virol.* 65: 5289-5296.
 94. Nelson, J. A., Reynolds-Kohler, C., Oldstone, M. B. A., and Willey, C. A. 1988. HIV and HCMV coinfect brain cells in patients with AIDS. *Virology* 165: 6371-6375.
 95. O'Hare, P., Goding, C. R., and Haigh, A. 1988. Direct combinatorial interaction between a herpes simplex virus regulatory protein and a cellular octamer-binding factor mediates specific induction of virus immediate-early gene expression. *EMBO J.* 7: 4231-4238.
 96. Orchard, K., Perkins, N., Chapman, C., Chapman, C., Harris, J., Emery, V., Goodwin, G., Latchman, D., and Collins, M. 1990. A novel T-cell protein which recognizes a palindromic sequence in the negative regulatory element of the human immunodeficiency virus long terminal repeat. *J. Virol.* 64: 3234-3239.
 97. Ostrove, J. M., Leonard, J., Weck, K. E., Rabson, A. B., and Gendelman, H. E. 1987. Activation of human immunodeficiency virus by herpes simplex virus type 1. *J. Virol.* 61: 3726-3732.
 98. Paya, C. V., Virelizier, J.-L., and Michelson, S. 1991. Modulation of T-cell activation through protein kinase C- or A-dependent signaling pathways synergistically increases human immunodeficiency virus long terminal repeat induction by cytomegalovirus immediate-early proteins. *J. Virol.* 65: 5477-5484.
 99. Payne, L. N. 1982. Biology of Marek's disease virus and the herpesvirus of turkeys. pp. 347-431. *In: Herpesvirus*, vol. 1 (Roizman, B. ed.), Plenum, New York.
 100. Perera, L. P., Mosca, J. D., Ruyechan, W. T., and Hay, J. 1992. Regulation of varicella-zoster virus gene expression in human T lymphocytes. *J. Virol.* 66: 5298-5304.
 101. Perera, L. P., Kaushal, S., Kinchington, P. R., Mosca, J. D., Hayward, G. S., and Straus, S. E. 1994. Varicella-zoster virus open reading frame 4 encodes a transcriptional activator that is functionally distinct from that of herpes simplex virus homolog ICP27. *J. Virol.* 68: 2468-2477.
 102. Peters, W. P., Kufe, D., Schlom, J., Frankel, J. W., Prickett, C. O., Groupe, V., and Spiegelman, S. 1973. Biological, and biochemical evidence for an interaction between Marek's disease herpesvirus and avian leukosis virus *in vivo*. *Proc. Natl. Acad. Sci. U.S.A.* 70: 3175-3178.
 103. Pulaski, J. T., Tieber, V. L. and Coussens, P. M. 1992. Marek's disease virus-mediated enhancement of avian leukosis virus gene expression and virus production. *Virology* 186: 113-121.
 104. Quinlivan, E. B., Holley-Guthrie, E., Mar, E. C., Smith, M. S., and Kenney, S. 1990. The Epstein-Barr virus BRLF1 immediate-early gene product transactivates the human immunodeficiency virus type 1 long terminal repeat by a mechanism which is enhancer independent. *J. Virol.* 64: 1817-1820.
 105. Quinn, T. C., Piot, P., McCormick, J., Feinsod, F. N., Taelman, H., Kapita, B., Stevens, W., and Facui, A. S. 1987. Serologic and immunologic studies in patients with AIDS in North America and Africa. *J. Am. Med. Assoc.* 257: 2617-2621.
 106. Quinnan, G. V., Masur, H., Rook, A. H., Armstrong, G., Frederick, W. R., Epstein, J., Manishewitz, J. F., Macher, A. M., Jackson, L., Ames, J., Smith, H. A., Parker, M., Pearson, G. R., Parrillo, J., Mitchell, C., and Straus, S. E. 1984. Herpesvirus infections in the acquired immune deficiency syndrome. *J. Am. Med. Assoc.* 252: 72-77.
 107. Rando, R. F., Srinivasan, A., Feingold, J., Gonczol, E., and Plotkin, S. 1990. Characterization of multiple molecular interactions between human cytomegalovirus (HCMV) and human immunodeficiency virus type 1 (HIV-1). *Virology* 176: 87-97.
 108. Reubel, G. H., George, J. W., Barlough, J. E., Higgins, J., Grant, C. K., and Pedersen, N. C. 1992. Interaction of acute feline herpesvirus-1 and chronic feline immunodeficiency virus infections in experimentally infected specific pathogen free cats. *Vet. Immunol. Immunopathol.* 35: 95-119.
 109. Rice, S. A. and Knipe, D. M. 1990. Genetic evidence for two distinct transactivation functions of the herpes simplex virus α protein ICP27. *J. Virol.* 64: 1704-1715.
 110. Roizman, B. and Batterson, W. 1985. Herpesviruses and their replication. pp.497-526. *In: Virology* (Fields, B. N. ed.), Raven, New York.
 111. Rosen, C. A., Sodroski, J. G., and Haseltine, W. A. 1985. The location of cis-acting regulatory sequences in the human T cell lymphotropic virus type III (HTLV-III/LAV) long terminal repeat. *Cell* 41: 813-823.
 112. Rosenberg, Z. F. and Fauci, A. S. 1991. Immunopathogenesis of HIV infection. *FASEB J.* 5: 2382-2390.
 113. Ruddell, A. M. 1995. Transcription regulatory elements of the avian retroviral long terminal repeat. 1995. *Virology* 206: 1-7.
 114. Ryden, T. A. and Beemon, K. 1989. Avian retroviral long terminal repeats bind CCAAT/enhancer-binding protein. *Mol. Cell. Biol.* 9: 1155-1164.
 115. Ryden, T. A., Mars, M., and Beemon, K. 1993. Mutation of the C/EBP binding sites in the Rous sarcoma virus long terminal repeat and gag enhancers. *J. Virol.* 67: 2862-2870.
 116. Sandri-Goldin, R. M. 1991. Analysis of the regulatory activities of the HSV-1 α protein ICP27. pp. 77-103. *In: Herpesvirus Transcription and Its Regulation* (Wagner, E. K. ed.), CRC, Boston.
 117. Sandri-Goldin, R. M. and Mendoza, G. E. 1992. A herpes virus regulatory protein appears to act posttranscriptionally by affecting mRNA processing. *Genes Dev.* 6: 848-863.
 118. Sealy, L. and Chalkley, R. 1987. At least two nuclear proteins bind specifically to the Rous sarcoma virus long terminal repeat enhancer. *Mol. Cell. Biol.* 7: 787-798.
 119. Sears, R. and Sealy, L. 1992. Characterization of nuclear proteins that bind the EFII enhancer sequence in the Rous sarcoma virus long terminal repeat. *J. Virol.* 66: 6338-6352.
 120. Sheridan, P. L., Sheline, C. T., Milocco, L. H., and Jones, K.

- A. 1993. Tat and HIV-1 promoter: a model for RNA-mediated regulation of transcription. *Semin. Virol.* 4: 69–80.
121. Skolnik, P. R., Pomerantz, R. J., De La Monte, S. M., Lee, S. F., Hsiung, G. D., Foos, R. Y., Cowan, G. M., Kosloff, B. R., Hirsh, M. S., and Pepose, J. S. 1989. Dual infection of retina with human immunodeficiency virus type 1 and cytomegalovirus. *Am. J. Ophthalmol.* 107: 361–372.
122. Smiley, J. R., Panning, B., and Smibert, C. A. 1991. Regulation of cellular genes by HSV products. pp. 152–174. *In: Herpesvirus Transcription and Its Regulation* (Wagner, E. K. ed.), CRC Press, Boston.
123. Smith, C. A., Bates, P., Rivera-Gonzalez, R., Gu, B., and DeLuca, N. A. 1993. ICP4, the major transcriptional regulatory protein of herpes simplex virus type 1, forms a tripartite complex with TATA-binding protein and TFIIB. *J. Virol.* 67: 4676–4687.
124. Sparger, E. E., Shacklett, B. L., Rental-Gegg, L., Barry, P. A., Pedersen, N. C., Elder, J. H., and Luciw, P. A. 1992. Regulation of genes expression directed by the long terminal repeat of the feline immunodeficiency virus. *Virology* 187: 165–177.
125. Spector, S. A., Hirata, K. K., and Neuman, T. R. 1984. Identification of multiple cytomegalovirus strains in homosexual men with acquired immunodeficiency syndrome. *J. Infect. Dis.* 150: 953–956.
126. Thompson, F. J., Elder, J., and Neil, J. C. 1994. Cis- and trans-regulation of feline immunodeficiency virus: identification of functional binding sites in the long terminal repeat. *J. Gen. Virol.* 75: 545–554.
127. Tieber, V. L., Zalinskis, L. L., Silva, R. F., Finkelstein, A., and Coussens, P. M. 1990. Transactivation of the Rous sarcoma virus long terminal repeat promoter by Marek's disease virus. *Virology* 179: 719–727.
128. Treisman, R. 1985. Transient accumulation of c-fos RNA following serum stimulation requires a conserved 5' element and c-fos 3' sequences. *Cell* 42: 889–902.
129. Vlach, J., and Pitha, P. M. 1992. Herpes simplex virus type 1-mediated induction of human immunodeficiency virus type 1 provirus correlates with binding of nuclear proteins to the NF- κ B enhancer and leader sequence. *J. Virol.* 66: 3616–3623.
130. Wagner, E. K. 1991. Herpesvirus transcription: General aspects. pp. 1–16. *In: Herpesvirus Transcription and Its Regulation* (Wagner, E. K. ed.), CRC, Boston.
131. Walker, S., Hagemeier, C., Sissons, J. G. P., and Sinclair, J. H. 1992. A 10-base-pair element of the human immunodeficiency virus type 1 long terminal repeat (LTR) is an absolute requirement for transactivation by the human cytomegalovirus 72-kilodalton IE1 protein but can be compensated for by other LTR regions in transactivation by the 80-kilodalton IE2 protein. *J. Virol.* 66: 1543–1550.
132. Wang, J., Jones, C., Norcross, M., Bohnlein, E., and Razzaque, A. 1994. Identification and characterization of a human herpesvirus 6 gene segment capable of transactivating the human immunodeficiency virus type 1 long terminal repeat in an Sp1 binding site-dependent manner. *J. Virol.* 68: 1706–1713.
133. Ward, P. L. and Roizman, B. 1994. Herpes simplex genes: the blueprint of a successful human pathogen. *T. I. G.* 10: 267–274.
134. Watson, R. J. and Clements, J. B. 1980. A herpes simplex virus type 1 function continuously required for early and late virus RNA synthesis. *Nature (Lond.)* 285: 329–330.
135. Wilson, A. C., LaMarco, K., Peterson, M. G., and Herr, W. 1993. The VP16 accessory protein HCF is a family of polypeptides processed from a large precursor protein. *Cell* 74: 115–125.
136. Wirth, U. V., Fraefel, C., Vogt, B., Vlcek, C., Paces, V., and Schwyzer, M. 1992. Immediate-early RNA 2.9 and early RNA 2.6 of bovine herpesvirus 1 and 3' coterminal and encode a putative zinc finger transactivator protein. *J. Virol.* 66: 2763–2772.
137. Yeung, K. C., Stoltzfus, C. M., and Stinski, M. F. 1993. Mutations of the human cytomegalovirus immediate-early 2 protein defines regions and amino acid motifs important in transactivation of transcription from the HIV-1 LTR promoter. *Virology* 195: 786–792.
138. Yuan, R., Bohan, C., Shiao, F. C. H., Robinson, R., Kaplan, H. J., and Srinivasan, A. 1989. Activation of HIV LTR-directed expression: analysis with pseudorabies virus immediate early gene. *Virology* 172: 92–99.
139. Zhou, Y. I., Chang, C. K., Qian, G., Chandran, B., and Wood, C. 1994. Trans-activation of the HIV promoter by a cDNA and its genomic clones of human herpesvirus-6. *Virology* 199: 311–322.