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1. Introduction

1.1 Latency and reactivation of HIV-1

Since the discovery of human immunodeficiency virus type 1 (HIV-1), there has been a great deal of interest in identifying cofactors that might accelerate the stages of development associated with acquired immunodeficiency syndrome (AIDS). Many environmental agents, namely inherent factors such as ethnicity and geographical location, were first implicated as risk factors in the study of HIV infection. However, speculation that infectious diseases may act as cofactors in HIV infection began to be studied soon thereafter. These speculations led to one of the early opinions that HIV plays a correlary role in AIDS, but not a causative role (Duesberg, 1989). AIDS patients have a history of both circumstantial serological and microbial evidence of increased exposure to a number of common and opportunistic infectious agents. It is difficult to ascertain, however, whether these various coinfections contribute anything to the progressive decline of the immune system (Pedersen et al., 1990). In vivo, infection with HIV-1 is followed by a long disease-free period, during which a low number of CD4+ mononuclear leukocytes (CCR5 coreceptor positive monocytes and CXCR4 coreceptor positive lymphocytes) containing transcriptionally silent integrated provirus can be found. HIV-1 replication can be demonstrated in only a small population of T cells without inducing clinical manifestations. This state of latency is partly due to low transcriptional activity of the integrated provirus in resting cells. Activation of CD4+ cells by antigens, mitogens (Tobiume et al., 1998) or superinfection by other viruses interacting with HIV-1 via viral and/or cellular transacting factors may terminate HIV-1 latency, leading to a productive HIV-1 infection. Transactivation of the HIV-1 long terminal repeat (LTR) in turn will induce gene expression, including the synthesis of the HIV-1 transactivator protein (TAT) (Arya et al., 1985). TAT will then independently amplify HIV-1 gene expression, ultimately leading to a high level of virus replication and death of infected cells. Onset and progression of AIDS correlates with augmented production of infectious virions parallel to a...
shift in their tropism from CCR5 towards the CXCR4 coreceptor. The number and ratio of infected cells, mainly CD4+ T lymphocytes, increases 100-1000-fold during this period (Ensoli et al., 1989).

Initiation and augmentation of transcription by HIV relies not only on the simultaneous binding of virus-encoded TAT polypeptide to TAR, but the normal cellular transcriptional factors (NF-κB, Sp1, and other regions of the 3' HIV-1 mRNA start site) also anchor into specific binding sites of the proviral LTR. The production of such factors are augmented after mitogen treatment followed by signal transduction from cell surface receptors and through several parallel pathways including secondary messenger systems (Martin et al., 1991; Mosca et al., 1987a, 1987b; Nabel & Baltimore, 1987; Siekiewitz et al., 1987). The basal level promoter activity does not require binding of NF-κB or other nuclear factors (Wang et al., 1994).

1.2 The role of heterologous viruses in HIV-1 activation

Two alternative ways exist for HIV transactivation by heterologous viruses. First, two (or more) viruses can simultaneously infect the same immune cell if the appropriate receptors are expressed on its surface. Several DNA viruses have been suggested as potential cofactors in AIDS due to their capability to transactivate in vitro the HIV-1 LTR-directed gene expression by a tat-independent mechanism. For example, herpes simplex virus type 1 (HSV-1) immediate early gene products ICP0 and ICP4 act via NF-κB and Sp1 (Mosca et al., 1987a, 1987b). Stimulating effects vary by cell type, indicating that the cellular environment plays an important role in viral transactivation (Albrecht et al.,1989). HSV-2 can coinfect, simultaneously replicate and transactivate HIV-1 (Kucera et al., 1990). Human cytomegalovirus (HCMV) IE genes activate via Sp1 and NF-κB sites (Davis et al., 1987; Ghazal & Nelson, 1993). HCMV also transactivates HIV-2 LTR (Duclos et al., 1989). Epstein-Barr virus (EBV) EBNA2, BRLF1 and LMP gene products act through NF-κB and Sp1 (Hammarskjöld et al., 1992; Kenney et al., 1988; Quinlivan et al., 1990). The IE protein of pseudorabies virus induces the overproduction of Sp1 (Yuan et al., 1989). Papovaviruses (JC, BK) transactivate through Sp1 (Gendelman et al., 1986), adenovirus (AdV) E1A 13S protein exerts activation on the TATA box and Sp1 sites (Nabel et al., 1988; Rice & Mathews, 1988). Vaccinia virus (Stellrecht et al., 1992), hepatitis B virus (HBV) X protein (Seto et al., 1988), and a retrovirus named human T lymphotropic virus type I (HTLV-I) tax polypeptide (Siekiewitz et al., 1987) transactivate HIV-1. Lymphoid cells chronically infected with HTLV-I are more susceptible to infection in vitro with HIV-1, and coinfectected cells produce higher levels of HIV-1 (De Rossi et al., 1986, Ongrádi et al., 2000b). It is likely that the activation of HIV-1 by heterologous viruses in dually infected cells results from the cumulative effects of various gene promoters. None of these viruses infects CD4+ T cells as their primary target. Their gene products do not bind directly to the HIV LTR sequences, and there is no apparent molecular link between these products and cellular transcriptional factors. Intracellular transactivation is mediated by those transcriptional factors that are upregulated upon external stimuli. They may act in a paracrine manner, whereby altering mediator production affects the producer cell or neighbouring cells. It has been established that tumor necrosis factor (TNF)-α via NF-κB activation acts in tandem with HSV-1 in augmenting HIV-1 in different CD4+ cells such as T lymphocytes, monocytes, and leukemic cell lines (Popik & Pitha, 1994). Thus, the relevance of these viruses to direct HIV-1 activation in vivo is still waiting for unequivocal confirmation. Simultaneous infection in a single cell is a relatively rare event, and as such the biological effects of an event of this nature could be minimal. On
the contrary, cross-talk between immune cells carrying different viruses is more common, especially in lymph nodes where they are in the vicinity of one another. Heterologous viruses can infect many other types of cells which are not targets of HIV, but release several immunomodulating mediators. This transcellular transactivation can last a lifetime, and its intensity may vary on an individual basis, as well as on the synergistic or antagonistic effects of several factors including the heterologous viruses themselves. This category of interaction seems to have a more significant biological and clinical impact on HIV replication and AIDS progression. Expression of the early and/or immediate early genes of several heterologous viruses exert very strong modifying effects on the normal mediator pattern, which consequently alters HIV replication. HIV infected individuals carrying other viruses, therefore, may be at a greater risk for early onset and rapid progression of AIDS.

2. Human herpesvirus 6 as a broad-range virus transactivator

2.1 Characterization and genetic structure of HHV-6

Among heterologous viruses, human herpesvirus 6 (HHV-6, Herpesviridae family, Betaherpesvirinae subfamily, Roseolovirus genus) seems to be one of the most important HIV-1 transactivator. HHV-6 is predominantly a T cell tropic virus, and its unique immunomodulatory characteristics have made it a widely studied in vitro and in vivo model. HHV-6 has two variants, which differ on the basis of distinct genetic, immunological and biological characteristics; Variant A (HHV-6A) was originally obtained from the peripheral blood mononuclear cells (PBMC’s) of patients with HIV infection and other lymphoproliferative disorders (Salahuddin et al., 1986), while HHV-6B was originally obtained from the PBMC’s of children suffering from exanthema subitum. Isolates were later grouped according to prototypes (e.g. GS and U1102 for HHV-6A, Z29 and HST for HHV-6B) (Ablashi et al., 1991). The viral genome is 160-162 kbp in size and is formed by a central unique (U) region (143-145 kbp) flanked at both ends by terminal direct repeats (DR, each 8-9 kbp long). The DR’s contain a tandem repetitive sequence that is also present in human telomeres (Thomson et al., 1994a). The genome of HHV-6B contains 119 open reading frames (ORFs) encoded by 97 genes, 9 of which are absent in HHV-6A: DR4, DR5, DR8, U1, U61, U78, U88, U92, U93 (Domingu ez et al., 1999; Gompels et al., 1995). Several conserved genes organized into 7 blocks are present in the genome of all herpesviruses. One additional block comprises 17 genes conserved in all Roseoloviruses (U20-21, U23-24, U26, U85, U100). Two genes are unique to HHV-6 and present in both variants: U83, which encodes chemokines (Dewin et al., 2006), and U94, which encodes for a homologue of the human adeno-associated virus type 2 (AAV-2) rep gene (Thomson et al., 1994b). The latter is transcribed in latently infected lymphocytes, suggesting it likely contributes to the maintenance of latency (Rotola et al., 1999). The overall nucleotide sequence identity between HHV-6A and –B variants is 90%, but the genes of DR, U86-U93, and U95-100 show the highest degree of sequence divergence, reaching 72%. Increased divergence in consequent amino acid sequences explains the biological and pathogenic differences between variants A and B. Differences in the U100 gene products, designated gQ, determine differences in cell tropism between variants (Mori et al., 2003). The variants also differ in temporal regulation and splicing patterns of U91 transcripts in T cell lines (Mirandola et al., 1998). The products of U90 and U95 genes are hypothesized to play a role in the establishment of variant–specific niches within the host. The degree of heterogeneity between HHV-6 isolates within the same variant is less than 1% (Ablashi et al., 1991). In the
isolates obtained from immunocompetent persons no genetic gradients and recombinants between HHV-6A and HHV-6B have been detected, making it clear that the two variants have independent biological niches and meet the criteria for classification into distinct species (Dominguez et al., 1999).

2.1.1 Molecular interactions between HHV-6 and the immune system

2.1.1.1 Modulation of surface receptor expression, cytokine and chemokine pattern

CD46 has been demonstrated as a cellular receptor for both HHV-6A and HHV-6B (Santoro et al., 1999). This glycoprotein is a complement regulator, and is expressed on the surface of all nucleated cells. Binding of HHV-6A gH structural polypeptides, but not HHV-6B gB structural polypeptides, to CD46 cell surface receptors induces the downregulation of IL-12 and CD46 with consequent disturbances in the complement system (Santoro et al., 1999), cell fusion, and CD4+ T lymphocyte depletion (Mori et al., 2002). Through CD46, HHV-6 has the ability to infect a wide variety of cell types including neuronal cells (references in De Bolle et al., 2005), but both variants express a non-naive phenotype and replicate most efficiently in CD4+ T lymphocytes (Ablashi et al., 1991; Grivel et al., 2003). This phenotype introduces a unique relationship to the immune system with profound implications on immunomodulation. They also infect monocyte/macrophages (Kondo et al., 1991) and dendritic cells (Kakimoto et al., 2002) to further establish their latent infection. HHV-6A efficiently infects CD8+ T cells (Lusso et al., 1991), γδ lymphocytes (Lusso et al., 1995), and natural killer (NK) cells (Lusso et al., 1993). This leads to the induction of CD4 expression on infected cells, which in turn potentially increases the range of cells susceptible to HIV infection. The genes responsible for transactivation of the CD4 promoter include U86 and U89 (Flamand et al., 1998). HHV-6A and HHV-6B viral envelope proteins inhibit T lymphocyte proliferation induced by phytohemagglutinin (PHA), IL-2 or antigens (Horvat et al., 1993). Not only do the infected cells experience programmed cell death (apoptosis), but adjacent healthy lymphocytes die as well due to high concentrations of both TNF-α and -β released from nearby infected cells (Inoue et al., 1997). Both variants inhibit the expression of CD3/T cell receptor (TCR) complex (Lusso et al., 1991), the lectin-like receptor DC-SIGN on dendritic cells (Niiya et al., 2004), CD14, CD64 and HLA-DR on antigen presenting cells (Janelle & Flamand, 2006).

HHV-6 profoundly modifies the bodily pattern of cytokine and chemokine production as well, which in turn significantly affects the functionality of effective immune responses. HHV-6A strongly inhibits IL-12 and IFN-γ production, consequently lowering the output of uninfected T lymphocytes (Arena et al., 1999). IL-12 production by macrophages (Smith et al., 2003), IL-2 production by CD4+ lymphocytes (Flamand et al., 1995), IL-2, IFN-γ production by HSB-2 cultures (Ongrádi et al., 1990), IL-10 and IL-14 production in SupT1 cultures is inhibited (Mayne et al., 2001). On the contrary, HHV-6A upregulates the production of IL-1β, IFN-α, TNF-α, IL-10 synthesis in PBMC’s, TNF-α production in HSB-2 cultures, IL-10, IL-12 production in monocytes, and IL-15 production in both monocytes and NK cells (Arena et al., 1997, 1999, 2000; Flamand et al., 1990, 1991, 1996; Kikuta et al., 1990; Mayne et al., 2001; Li et al., 1997; Ongrádi et al., 1990). HHV-6A induces GM-CSF in the peripheral blood lymphocytes and the ensuing increase in macrophages consequently enhances differentiation of bone marrow progenitor cells, further sensitizing them to HIV infection (Furlini et al., 1996). All these changes result in a Th1 to Th2 shift in cytokine pattern, an impairment of cellular immunity and maintenance of persistent viral infections.
Similar to HHV-6A, HHV-6B increases expression of IL-18, IL-2 receptor and members of TNF-α superfamily receptors (Mayne et al., 2001). HHV-6B increases the production of IFN-α in PBMC’s (Kikuta et al., 1990), IL-8 release from HepG2 human hepatoma cell lines without altering IL-1β expression (Inagi et al., 1996), and downregulates IL-12 production (Smith et al., 2001). Upon HHV-6B infection, the cytokine pattern produced by MOLT-3 CD4+ lymphoid cells drastically changes as compared to mock-infected cultures in synergism with IL-2, while the concentration of IL-3, IL-4, IL-10, IL-15, GM-CSF, TNF-α and -β decreases. These changes result in the suppression of innate, humoral and cellular immunity in vivo (Ongrádi et al., 2006).

It seems that the global effect of HHV-6 on human immune functionality differs by variant. HHV-6A targets the suppression of cellular immunity above all, while HHV-6B primarily weakens humoral immunity. The consequence of variant-specific immunomodulation is the onset of different clinical entities and provision of helper function for other viral diseases. These studies have suggested that HHV-6A induced chronic immune alterations contribute to HIV pathogenesis and AIDS progression as causative factors, while recurrent HHV-6B infection acts as a secondary contributor by aggravating and accentuating other immunocompromised conditions.

2.1.1.2 HHV-6 encoded chemokines and chemokine receptors

During co-evolution with animals, HHV-6 seems to have obtained genes from them via molecular piracy. The products of these genes may play important roles in pathogenesis and immune evasion. U83 of HHV-6B encodes for a functional β-chemokine (Zou et al., 1999). This protein is produced by infected cells, and as a highly active CCR2 agonist attracts CCR2-expressing cells such as monocytes/macrophages the virus establishes new infection, thus facilitating the spread of the virus. U83 of HHV-6A encodes for two different forms of β-chemokines. The full-length form acts as an agonist while the spliced form acts as an antagonist that interacts with other chemokine receptors, i.e. CCR1, CCR4, CCR5, CCR6 and CCR8, and is expressed in T cells, monocytes/macrophages, and dendritic cells (Dewin et al., 2006). Gene U22 also codes for yet another chemokine (French et al., 1999). Counterparts of U12 and U51 genes have been shown in the betaherpesviruses and they code for G-protein coupled receptor homologs: U12 protein of both variants acts as a β-chemokine (RANTES, macrophage inflammatory protein /MIP/-1α and -1β, monocyte chemotactic protein /MCP/-1) binding receptor related to CCR1, CCR3, and CCR5. It is expressed at the late stage of infection of monocyte/macrophages and cord blood mononuclear cells. Its expression is activated by the above cytokines elicited on the effect of other factors, i.e. viruses, but not by the α-chemokine IL-8 (Isegawa et al., 1998, Kondo et al., 2002). While expressed on human epithelial cells, U51 protein specifically binds and down-regulates RANTES (Caruso et al., 2003; Milne et al., 2000) by mimicking receptors typically expressed on the surface of activated T cells (Menotti et al., 1999). Down-regulation of RANTES may consequentially compromise the ability of T-lymphocytes, monocytes and eosinophils to gather at sites of inflammation. The gene product of U51 may act as a positive regulator of viral replication, possibly promoting membrane fusion and facilitating cell-to-cell spread (Zhen et al., 2005).

The main task of the production of HHV-6 specific chemokines and chemokine receptors is to ensure the efficient dissemination of virus throughout the organism either by way of acute infection or latent carriage.

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2.2 Clinical manifestations and transactivating potential of HHV-6A

The exact mode of transmission and pathomechanism of HHV-6A have not been established. In developed countries, HHV-6A does not or very rarely infects children, but from adolescence onward its prevalence increases. In several countries of the developing world, especially in Sub-Saharan and South Africa, as much as one quarter of children below the age of 18 months already carries this variant in both HIV-1 positive and negative groups. This suggests that early infections have a different exposure profile compared to North America and Europe (Kasolo et al., 1999). In a recent study of genotyping, variant A was identified in 85% of HHV-6 infections of asymptomatic African infants, and HHV-6B was largely detected as a co-infection alongside HHV-6A (Bates et al., 2009). In such cases, unusual recombinants between HHV-6A and HHV-6B were shown (Gompels & Kasolo, 2006; Kasolo et al., 1997). This is reminiscent of the peculiar adenovirus recombinants found in the intestines of AIDS patients (Hierholzer et al., 1988). The molecular mechanisms are known in neither case, but each raise the idea of a common effect exerted by HIV-1. Saliva and breast milk contained neither HHV-6A virions nor viral DNA. It was found in 54% of the lungs of healthy adults (Cone et al., 1996). In the blood of children born to HIV seropositive mothers living in Africa, a high-quantity load of HHV-6A can be detected. HHV-6 DNA has been found in the semen of two thirds of healthy males, and although its variant specificity has not been established, epidemiological circumstances raise the possibility of sexual spread. Transmission is also suspected to occur from mother to child (Bates et al., 2009). The symptoms of acute infection are unknown, but in some well-documented cases febrile conditions in children were observed. Primary adult infections have been associated with severe inflammatory or neurological disease with increased neurotropism (Alvarez-Lafuente et al., 2007; Hall et al., 1998; Portolani et al., 2005). Persistent HHV-6A infection in the brain may also contribute to AIDS-associated dementia. Primary HHV-6A infection later in life may trigger the onset of multiple sclerosis (MS) (Akhyani et al., 2000; Alvarez-Lafuente et al., 2006; Ongrádi et al., 1999). HHV-6A also establishes life-long latency in CD4+ immune cells, and is usually reactivated in immunocompromised patients after bone marrow or organ transplantation along with HHV-6B, HHV-7 and HCMV (Griffiths et al., 1999). HHV-6A might be a cofactor in the progression of several tumors. The simultaneous detection of HHV-6A and human papilloma virus type 16 (HPV-16) in cervical carcinoma cells (Chen et al., 1994b) and the ability of HHV-6A U16 and U30 gene products to transactivate E6 and E7 of HPV-16 in cervical epithelial cells (Chen et al., 1994a) have prompted investigation of its role in the pathogenesis of cervical carcinoma. In a large clinical study, it was concluded that although HHV-6A is not the causative agent of cervical carcinoma, it can contribute to multistage carcinogenesis and the progression of cervical cancer (Di Paolo et al., 1994). It is of note that cervical cancer is one of the AIDS criteria. Furthermore, due to their high prevalence in the lymphoid tissues, HHV-6 and EBV are frequently detected simultaneously (Bertram et al., 1991). HHV-6A infection has been shown to activate EBV replication from latency by a mechanism of transactivation that targets a cyclic AMP response element with the EBV Zebra promoter (Flamand & Menezes, 1996) to increase expression of EBV early genes (Cuomo et al., 1995) and to enhance the transformative capacity of EBV (Cuomo et al., 1998). In return, the presence of EBV renders B cells susceptible to HHV-6 infection. EBV has been detected in all brain lymphomas and frequent detection occurs in other lymphomas of AIDS patients as well (Cuomo et al., 1995). HHV-6A has been shown to enhance the progression of lymphomagenesis. As mentioned earlier, the HHV-6A U94 gene product, known as the
RepH6 polypeptide, is able to complement replication of a rep-deficient AAV-2 genome (Thomson et al., 1994b). Contrary to HIV LTR activation by HHV-6, HHV-6 cannot transactivate latent infection by human T lymphotropic virus type I (HTLV-I) or subsequently affect the expression of its tax transactivator gene (Cao & Sullivan, 1992). Mediators released from actively replicating HHV-6A or carrier cells transactivate the human endogenous retrovirus (HERV) K18 and induce expression of HERV K18-encoded superantigen (Tai et al., 2009). HHV-6B also induces HERV K18-encoded superantigen expression (Turcanova et al., 2009).

In rare clinical manifestations of HHV-6A infection (e.g. hepatitis) or transmission by organ transplantation in Europe, North-America and Japan (Portolani et al., 2005; Potenza et al., 2008) where HHV-6B predominates, HHV-6A strains may be considered emergent infectious diseases. These cases will require careful genotyping as well as viral load and gene expression studies to further characterize the infection (Bates et al., 2009).

2.3 Epidemiology and biological effects of HHV-6B

Although both HHV-6 variants infect CD4+ immune cells, and despite their high molecular homology they profoundly differ in epidemiology and pathogenesis. Lack of reliable serological testing has hindered their differentiation in pathological conditions for several decades, but variant specific polymerase chain reaction (PCR) and other PCR based quantitative methods have yielded satisfactory data on their role played in acute and chronic diseases. The mode of transmission and pathomechanism of HHV-6B has sine been well-characterized, and evidence seems to indicate that humans are the only know reseros of HHV-6B. The salivary gland serves as a reservoir for symptomless shedding, and the saliva of the caregivers of small children has been shown to transmit infection via droplets (Fox et al., 1990). By age 2, almost all children have become seropositive (references in Ongrádi et al., 1999d). The majority of infections are symptomless, but approximately 15% of infected children develop exanthema subitum (Yamanishi et al., 1988). Although HHV-6B DNA sequences were found in the genital tract of 20% of pregnant women, perinatal transmission is unlikely (Okuno et al., 1995). HHV-6B establishes life-long latency in CD4+ immune cells. HHV-6B is frequently reactivated in immunocompromised conditions, e.g. after transplantation of bone marrow, liver, kidney or pancreas. High fever, graft rejection and other lethal complications are not uncommon. HHV-6B reactivation is followed by HHV-7 and HCMV reactivation in a temporal pattern, aggravating clinical symptoms (Herbein et al., 1996). HHV-6B might also act as a cofactor in the pathogenesis of several chronic debilitating immunological or neurological diseases such as Hodgkin’s lymphomas, multiple sclerosis, mesial temporal lobe epilepsy, chronic fatigue syndrome and drug induced hypersensitivity syndrome (references in Caselli & Di Luca 2007 and De Bolle et al., 2005). HHV-6B DNA is commonly detected in the brain of deceased AIDS patients and HHV-6B proteins are often located in the demyelinated areas, suggesting an active role in persistent infection and neurological complications in AIDS patients (Drobyski et al., 1994). No vaccination against HHV-6B exists, but for chemoprevention and treatment in severe conditions ganciclovir, valaciclovir, foscarinet and cidofovir have been used (references in Caselli & Di Luca, 2007 and De Bolle et al., 2005).

2.4 Chromosomally integrated HHV-6

It has recently been demonstrated that both variants of HHV-6 can integrate specifically into the telomeres of human chromosomes 1, 9, 10, 11, 17, 18, 19 and 22 of PBMC’s in vivo and in
HIV-Host Interactions

264

vitro (Luppi et al., 1993; Morrisette & Flamand, 2010; Torelli et al., 1995). This behavior is unique among human herpesviruses. The presence of human telomeric-like repeat sequences at the HHV-6 genome termini (Gompels & Macaulay, 1995) and the HHV-6 U94 gene product (RepH6) might mediate the site-specific viral DNA integration within human cells (Surosky et al., 1997). Chromosomally integrated HHV-6 (CIHHV-6) can be passed through the germ line. Recent evidence from studies in the USA, UK, and Japan have shown that approximately 0.2-0.85% of infants experience vertical transmission of HHV-6 through the germ line, accounting for almost all HHV-6 congenital infections with no significant differences between distribution of variants (Hall et al., 2008; Tanaka-Taya et al., 1996; Ward et al., 2006). Cells containing CIHHV-6 copies do not have closed circular viral DNA (episomes), but produce a high viral load in the blood (10^6-10^7 copies per ml). A person with CIHHV-6 will never be negative by PCR in serum or whole blood (Ward et al., 2006). While some individuals with CIHHV-6 are asymptomatic, the integrated virus appears to be capable of reactivating. Members of these families carry identical HHV-6 strains, and some of them suffer from severe neurological symptoms. It has been demonstrated that CIHHV-6 can be made to reactivate by chemically stimulating the integrated cells (Arbuckle et al., 2010). Several case reports have shown that CIHHV-6 patients with neurological problems responded to antivirals (Troy et al., 2008; Wittekind et al., 2010).

3. Transactivation of HIV by human herpesvirus 6 variant A and B

3.1 In vitro studies on the intracellular transactivation of HIV by HHV-6 variants

The fact that HHV-6 and HIV-1 infect overlapping subsets of CD4+ lymphocytes (Lusso & Gallo, 1995) and lytic HHV-6 infection may contribute to the decline of this cell population in HIV-infected individuals, has lead to the hypothesis that there is specific interaction between these viruses. To substantiate this claim, several arguments were initially raised based on in vitro data rather than on clinical observations. In the first logical investigation, freshly isolated and activated PBMC’s containing CD4+ immune cells were simultaneously infected with HIV-1 and HHV-6A (GS). It was demonstrated that HHV-6A and HIV-1 could productively coinfect individual CD+ T cells, resulting in accelerated HIV-1 gene expression and enhanced cell death through apoptosis (Lusso et al., 1989). Infection of the ACH-2 leukemic T cells carrying latent HIV-1 with HHV-6A resulted in HIV-1 antigen coexpression with early-late HHV-6 products, suggesting that more IE gene products are involved in the activation of latent HIV-1 (Isegawa et al., 2007). Superinfection of U1 promonocytic cells latently carrying HIV-1 occurred by introducing HHV-6A (GS) and treating with TNF-α induced massive HIV-1 replication, whereas none of the clinical isolates of HHV-6B were able to break latency of HIV-1. It is of interest that HIV-1 upregulation elicited by HHV-6 was not inhibited by anti-TNF-α antibodies (Knox & Carrigan, 1996). Cloned fragments of HHV-6 and HIV-1 LTR were cotransfected into different cells, and the transactivating potential of HHV-6 infection on HIV-1 LTR was reported (Ensoli et al., 1989). Since then, transactivating functions have been assigned to an increasing number of individual HHV-6 genes. The protein encoded by HHV-6A (U1102) DR7 gene, expressed from 18h postinfection has been shown to transactivate HIV-1 LTR promoter and increase HIV-1 replication ( Kashanchi et al., 1994, Thompson et al., 1994). Its oncogenic potential in NIH 3T3 fibroblast cells relates to its capacity for binding and initiating the tumor suppressor protein p53 (Kashanchi et al., 1997). The U3-encoded protein was found to transactivate the HIV-1 LTR promoter in money kidney CV-1 cells (Mori et al., 1998). The U16 to U19 genes
encode transactivators that upregulate viral and cellular transcription. The immediate early (IE) expressed spliced gene products of U16/U17 and the IE U18- and U19-encoded proteins have all been shown to independently transactivate the HIV-1 LTR promoter in vitro (Flebbe-Rehwaldt et al., 2000; Geng et al., 1992; Nicholas & Martin, 1994). The DNA polymerase processing factor, encoded by the HHV-6 (U1102) U27 gene, was shown to transactivate the HIV-1 LTR in CV-1 cells. The presence of NF-κB binding sites was mandatory for the response to pU27 (Zhou et al., 1994). The HHV-6 IE-A locus encodes two proteins, IE1 and IE2, corresponding to the ORFs U89 and U86-87, respectively. Both are expressed from spliced mRNAs, and each contains an exon derived from the U90 gene (Nikolaou et al., 2003). IE1 of HHV-6A was shown capable of transactivating heterologous promoters. Compared to the IE1 protein of HHV-6A, the HHV-6B IE1 protein was found to exhibit much lower transactivating potential on HIV-1 LTR (Gravel et al., 2002). IE2 activates multiple promoters that have no regulatory element in common, such as the complex HIV-1 LTR promoter, or simple promoters containing zero or only one response element (NF-κB, CRE, or NF-AT (Gravel et al., 1998). HHV-6A (U1102) U94-encoded RepH6 acts as a transactivator by binding to a transcription factor, human TATA binding protein (Mori et al., 2000). RepH6 by itself possesses single-stranded DNA binding capacity, which is enhanced by cellular nuclear factors (Dhepakson et al., 2002), and is known to activate the HIV-1 LTR promoter in fibroblast cells (Thomson et al., 1994b).

HHV-6 encoded proteins with HIV-1 LTR transactivating potential not only stimulate HIV-1 expression (Ensoli et al., 1989; McCarthy et al., 1998), but these proteins (e.g. IE1) and the HIV-1 transactivating protein TAT have been shown to interact synergistically in this respect as early as 6.5 hours after HHV-6 infection (Di Luca et al., 1991, Garzino-Demo et al., 1996). HIV-1 TAT enhances HIV-6A titers and protein synthesis in cord blood lymphocytes and continuous CD4+ JJHAN T cells (Sieczkowski et al., 1995), but no activation was detected in Jurkat cells (Di Luca et al., 1991). More products of genes and cloned gene fragments of HHV-6A (U1102), namely Sal I, EcoRI (encoding p41) genomic fragments and HHV-6A (GS) pZVB70 and pZVB10 transactivate HIV-1 LTR at the NF-κB site, while pZVH14 acts through the Sp1 site in African green monkey kidney cells (CV-1) and human T cells (Geng et al., 1992), although in other experiments all three fragments have been shown to activate NF-κB. HHV-6A is able to activate HIV LTR in both stimulated and resting T lymphocytes, while HHV-6B (Z29) can carry out HIV LTR activation in T cells only (Horvat et al., 1991).

Patients and clinically normal individuals are frequently infected with multiple viruses. It is therefore important to understand the implications of simultaneous infection by multiple viruses. Coinfections with HIV, HHV-6A and hepatitis C virus (HCV) are frequently seen in the same individual. In a recent study, human lymphoid cells were simultaneously infected with all three viruses. Individual cells were able to support replication of all three viruses without dominance of one virus. All these viruses are highly cytopathic, and therefore triply-infected cells were short lived (Salahuddin et al., 2007).

There are several reports concerning the inhibitory effect of HHV-6 on HIV-1 in cell cultures. Peripheral blood lymphocytes, macrophages, and dendritic cells were coinfected. Unfortunately, in the majority of these studies, two different HHV-6 strains belonging to variant B were used: either strain Z29 (Asada et al., 1999; Carrigan & Knox, 1990; Spira et al., 1990) or SF (Levy et al., 1990b). Their further studies on cytokines produced by HHV-6 B infected cells showed inconclusive results, because virus infection was not synchronized. In
this way, consecutive generations of viruses induced different cytokines at very different or overlapping time points.

3.2 In vitro studies on the transcellular transactivation of HIV by HHV-6A and B

Next, to study the possible transcellular transactivation of HIV by HHV-6A, Öngrádi et al. infected HSB-2 CD4+ T lymphocytes with HHV-6A (GS). Supernatants of the infected cells contained a myriad of mediators and newly produced virions, similarly to the serum of patients. At regular time intervals, supernatant samples were removed and filtered until virus-free. Meanwhile CEM-ss cells were infected with HIV-1 (IIB) at different multiplicities of infection (moi) and then mixed with HHV-6A-free supernatant samples. Next, HIV-1 production was quantitated by syncytia formation, reverse transcriptase (RT) activity and p24 antigen production. Supernatants obtained at 24 and 48 hours post-infection exerted the strongest HIV-1 activation. The smaller the HIV-1 inocula were, the higher activating effect was observed. This timing coincides with the expression of early HHV-6A genes. Elevated TNF-α, but suppressed IFN-γ production was exhibited, and IL-2 was found to have no role. Late supernatant samples obtained at the time of virion production showed slightly inhibited HIV production. Distinct cytokines and chemokines are produced in a sequential manner by the same cell. Their ratio continuously changes, and they furthermore exert pleiotropic effects. HIV-1 activation (and/or inhibition) via HHV-6 induced cytokine and chemokine production is the net effect of many soluble factors. This is the only known experiment in the literature describing that HHV-6 infected--but virus-free--media obtained from one type of CD4+ lymphoid culture modifies HIV-1 production in another lymphoid culture (Öngrádi et al., 1990, 1999c). Similarly, separated human peripheral blood monocytes were exposed to different viral antigens, and aliquots of the media of these monocytes were mixed to ACH-2 and U1 cells latently infected by HIV-1. Conditioned media obtained from HCMV and EBV antigen exposed monocyte cultures augmented HIV-1 replication, whereas others, such as HSV-1, HSV-2, VZV, HHV-6A failed to stimulate HIV-1 replication (Clouse et al., 1989). These suggest that HIV-1 is under several synergistic or antagonistic effects in vitro. Several studies have also shown that certain proinflammatory cytokines induced by HHV-6A infection--such as TNF-α, IL-1β and IL-6 enhance in vitro expression of HIV-1 (Flamand et al., 1991). The major mode of transcellular transactivation between HHV-6A (GS) infected and HIV-1 carrier lymphocytes is mediated by TNF-α and consequent NF-κB induction followed by its increased binding to LTR sequences. In vivo, HHV-6A induces the T helper cell profile to shift from Th1 to Th2 by upregulating IL-10 and downregulating IL-12 in infected PBMC’s (Arena et al., 1999), which might act with the similar effects of HIV-1 to accelerate AIDS progression.

4. Epidemiological studies on the HIV transactivating and AIDS promoting potential of HHV-6

4.1 Cross sectional molecular studies

In vivo transactivation of HIV-1 by HHV-6 has been postulated on the basis of several in vitro experiments. Following the discovery of HHV-6A, it was frequently isolated from HIV-1 infected patients worldwide (Dowling et al., 1987; Levy et al., 1990a; Lopez et al., 1988; Tedder et al., 1987) although no opportunistic diseases had been associated with HHV-6A at that time. Concomitant infection by HHV-6A, HTLV-I and HIV-2 has also been described (Agout et al., 1988). Widespread HHV-6A infection was documented in patients with AIDS.
at post-mortem examination (Carrigan & Knox, 1994). HHV-6A infected cells--usually lung macrophages--were observed in all patients, whereas HHV-6A infected lymphocytes and epithelial cells were seen in approximately two thirds of patients. The kidneys and liver also showed wide-spread infection of lymphocytes in inflammatory infiltrates. In the lymph nodes, HHV-6A concentrated in lymphocytes in the medullary region. Lymphoid organs are important reservoirs of HIV infection, and progression from HIV-1 infection to AIDS is associated with the involution of these tissues. Cell destruction is synergistically enhanced leading to early disintegration of the lymphoid environment with higher viral load. HIV proviral viral load was higher in tissues taken at autopsy if the organ also harbored HHV-6, which could suggest upregulation of the former by the latter (Corbellino et al., 1993; Knox & Carrigan, 1994a, 1996). HHV-6B levels in the lymph nodes and in different organs of deceased patients also were found elevated alongside increased HIV-1 loads. It has been postulated that neighbouring cells exert mutual effects by altered cytokine milieu (Emery et al., 1999). Excretion of HHV-6B in the saliva of patients in successive stages of the disease was not significantly different (Gautheret et al., 1995).

Ongrádi et al. also tested several groups of patients for double virus infection. In the first series of cross-sectional studies, patients in consecutive stages of HIV-1 infection with declining CD4+ cell number (symptomless, full blown and terminal AIDS, permanent HIV seronegative sexual partners, and control individuals) were screened for HHV-6A antibodies by immunofluorescence. As compared to controls, the mean level of IgM in the sexual partners raised 30-fold, that of IgG increased 10-fold, and 80% of individuals had low avidity IgG suggesting fresh HHV-6A infection. As compared to controls, the mean titer of IgM to HHV-6A remained elevated 10-fold in each group of HIV positive subjects. The highest level was found in the HIV seronegative partner group. The IgG level was 6-fold increased in asymptomatic HIV carriers, 4-fold in early and 5-fold in terminal AIDS patients. In the rapid progressors of AIDS patients HHV-6A IgG was higher, whereas in the subgroup of rapid progressors of terminal AIDS patients HHV-6A IgG was significantly lower compared to slow progressors. More than one quarter of AIDS patients had low avidity IgG to HHV-6A. These data suggest that, parallel to the decline of CD4+ T cell number and disease progression, HHV-6A maintains a chronic persistent infection in a significant number of HIV infected persons, and repeated HHV-6A infection furthermore occurs in the sexual partners of HIV-1 carriers. In the case of rapid progression, HHV-6A IgG production ceases (Maródi et al., 1998; Ongrádi et al., 1999b, 1999e), and as a result HHV-6A can become widely distributed by infiltrating the lymphocytes of several organs without specific tissue damaging effects (Knox & Carrigan, 1996).

Restricted expression of the same immediately early and early genes without the complete replication cycle, of several viruses can alter cellular machinery, resulting in malignant transformation and altering cytokine/chemokine production and subsequent HIV transactivation. The question then became whether simultaneous carriage of HIV-1 and HHV-6, or expression of viral genes reflecting active virus replication can influence depletion of CD4+ T cells and disease progression in different risk patients such as hemophiliacs and intravenous drug abusers (IVDA) compared to blood donors. DNA was extracted from plasma and peripheral blood lymphocytes (PBL’s), while RNA was only extracted from PBL’s. Carriage of both viruses was detected by PCR, and their expression by RT-PCR: PCR specific for HIV-1 env gene and nested PCR specific for HHV-6 ZVH14 fragment, was carried out. RT-PCR was carried out on complementer (c) DNA under the same conditions. The HHV-6 strain was characterised by endonuclease digestion fragments.
(Ceccherini-Nelli et al., Ongrádi et al. detected HHV-6A active replication more frequently in IVDA, 107/135, 79%), than in hemophiliacs (11/35, 31%, p<0.001) and blood donors (26/145, 18%, p<0.001). 81% of IVDA was positive by HIV-1 DNA PCR and, in spite of specific retroviral therapy, expressed HIV in 54% of cases. Furthermore, 43% (58/135) of these persons also expressed HHV-6 sequences evidently able to transactivate HIV-1. Expression of HHV-6 in HIV-1 seropositive patients is found to be 6.1 times more frequent than in HIV-1 seronegative counterparts. Simultaneous virus expression was shown to enhance CD4+ cell depletion. HHV-6 expression was found to enhance mortality of AIDS patients by approx. 35% in a two year period. These data prove that in the majority of patients HIV-1 expression is associated with active HHV-6A replication, but not with the latent state of HHV-6A. Among HIV-1 transactivating cofactors, HHV-6A seems to be relatively frequent. These data also suggest that the route of HHV-6A dispersal throughout the body is identical to that of HIV-1 (Ceccherini-Nelli et al., 1990; Ongrádi et al., 1994).

<table>
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<tr>
<th>Patients</th>
<th>CD4+ cell counts</th>
<th>HIV-1 viral load (log Eq/ml)</th>
<th>HHV-6 DNA PCR 1µg 5µg</th>
<th>HHV-7 DNA PCR 1µg 5µg</th>
<th>Clinical stage (CDC 1993)</th>
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Table 1. Clinical, virological and immunological data of HIV-1 seropositive patients

As outlined in Section V, HHV-7 shows a marked reciprocal interference with HIV-1 in vitro. To investigate in vivo interactions of HHV-6, HHV-7 and HIV-1, another cross-sectional study comprising 18 HIV-1 seropositive patients and 33 blood donors has been recently described (Barsanti et al., submitted). Presence of HHV-6 was established as above, and nested PCR for HHV-7 on DNA extracted from PBLs was carried out using a set of specific primers and probe designed from the KHR strain of HHV-7 as described (Okuno et al., 1995). HIV-1 load was quantitated by branched DNA signal amplification. Although no significant difference in HHV-6 prevalence was found between patients and controls (22 and
33%, respectively), all 4 HHV-6 positive patients belonged to variant A, whereas among controls with HHV-6 DNA positivity had variant A and 4 had variant B, confirming that HHV-6A is predominantly associated with immunocompromised patients (Table 1). The percentage of HHV-7 positivity in HIV-1 seropositive patients (39%) is significantly lower than that of blood donors (82%, \( p<0.01 \), \( \chi^2 \) test). HHV-7 positivity significantly correlated with a low level of HIV-1 (\( p<0.01 \), Mann-Whitney’s test) as compared to HHV-7 negative HIV-1 positive patients. Interestingly, while the presence of HHV-6A was detected in patients with all consecutive stages of HIV-1 infection, distributed evenly, HHV-7 positivity was found more frequently in patients with earlier stages of HIV-1 infection: namely stages A1- 3/3, A2-5/7, C2-1/1, B3-0/2, and C3-1/3. Although the number of patients in each group is very small, the trend is clear: independent or synergistic destruction of CD4+ T cells by HHV-7 and HIV-1 lead to their rapid declination. Another possibility is that rapid declination of CD4+ cells by HIV-1 prevents the replication of HHV-7 in the later stages of HIV-1 infection, but the low level of HIV-1 load argues against this hypothesis. Irrespective of interpretation, these results raise the idea that HHV-7 may not be such a harmless virus in HIV-1 infected patients. Further in vivo studies on the interaction between HIV-1 and HHV-7 are warranted (Barsanti et al., submitted).

4.2 Longitudinal, serological and molecular studies
Follow-up studies could be done only in a limited number of double infected patients, and methodology was the same as described above. The first study of HHV-6 infection was carried out in two HIV-1 seropositive patients to provide in vivo evidence of HHV-6 reactivation. Concomitant with a significant rise of anti-HHV-6 IgG detected by IFA, a transient increase in HHV-6 viral load was shown in PBL’s via PCR. During HHV-6 reactivation it was identified either as cell-free HHV-6 by PCR in plasma or by IgM antibody titers. HHV-6 reactivation was followed by a temporary decrease in CD4+ count and by a progressive dramatic loss of CD4+ cells during the 18 months post-reactivation. HHV-6 strain characterization by PCR demonstrated that the first patient (a woman with 232 CD4+ cell/mm\(^3\) at the beginning, 34 CD4+/mm\(^3\) with full-blown AIDS 16 months later) initially carried the B variant followed by reactivation and persistence of the A variant, while in the second patient (a man with 248 CD4+ at the beginning, then 14 CD4+/mm\(^3\), Pneumocystis carinii pneumonia and esophageal candidiasis 13 months later) only the A variant was detected. The evidence of HHV-6A reactivation presented suggests its involvement in a mechanism of immunologic damage underlying the disease by either direct destruction of lymphoid cells or altering cytokine pattern (Iuliano et al., 1997). In another longitudinal follow-up of two AIDS patients from active HHV-6A infection evidence was demonstrated but the profile of infection in the two patients varied. One patient demonstrated the appearance and disappearance of HHV-6A indicating viral reactivation, whereas the other patient exhibited chronic or persistent HHV-6A infection (Ablashi et al., 1997). In another cohort, serum samples and PBMC’s collected over a period of four years. IgG antibodies to HHV-6 gp110 late antigen did not differentiate between HIV-1 infected and control subjects, but IgG and IgM antibodies to p41/38 early antigens showed a significantly higher prevalence in HIV-1 infected individuals than in healthy donors, suggesting viral activation. HHV-6A was also shown in doubly infected PBL’s of T lineage (CD2+, CD4+, CD38+) (Ablashi et al., 1998b). As Ceccherini-Nelli et al., Ongrádi et al. demonstrated, others have also shown that HHV-6A is frequently reactivated in early asymptomatic HIV-1 infected patients (Secchiero et al., 1995). AIDS progression is accelerated in infants with vertically
acquired HIV-1 and early acquisition of HHV-6A infection (Kositanont et al., 1999). Periodic reactivation or sustained persistence seem to be general phenomena among doubly infected persons. Additionally, high HHV-6 antibody titers were demonstrated in patients with consistently increasing HIV-1 load (Lenette et al., 2005). HHV-6A upregulates CD4 expression, competitively inhibits binding of CCR5-trop HIV particles through RANTES overproduction, and ensures selective advantage of CXCR4-trop particles to infect T lymphocytes. HHV-6A persistence seems to sensitize the organism to HIV-1 infection. In the early phases of HIV infection, reactivated HHV-6A -especially in children- speeds up the disintegration of lymph nodes, as well as the onset and progression of AIDS in a vicious cycle. During the terminal phase of AIDS, a large amount of reactivated HHV-6A particles invade the whole body. In rapid AIDS progressors, both prevalence of HHV-6A virions and the titer of anti-HHV-6A antibodies are higher than in slow progressors. In AIDS-associated retinitis, HHV-6A proviral DNA, RNA and polypeptides are frequently shown beside HCMV (Qavi et al., 1989). In AIDS patients, HHV-6A might aggravate pneumonitis (Knox & Carrigan, 1994). Regarding the neuropathogenesis of HIV-1 infected children, HHV-6A is extensively disseminated in neural cells of the brain. It was reported that adult patients with AIDS had large areas of demyelination in their brain tissue at time of death (Knox & Carrigan, 1995).

5. Human herpesvirus 7 as a negative competitor of HIV infection

HHV-7 was isolated from the activated T lymphocytes of a healthy blood donor (Frenkel et al., 1990). HHV-6 and HHV-7 share similar genetic, biologic and immunologic features. HHV-7 also belongs to the *Roseolovirus* genus. The viral DNA is completely sequenced (Nicholas, 1996), it is formed by a unique segment of 133 kbp flanked by 6 to 10 kbp DR sequences, so that the genome length ranges between 145 and 153 kbp. Similar to HHV-6, the HHV-7 viral genome contains herpesvirus conserved genes arranged in 7 boxes. Nucleic acid sequence identity ranges from 20.7 to 75.7% in various genes, while amino acid sequence identity is between 41 and 75%. The coding ability of HHV-7 comprises 84 different ORFs (Megaw et al., 1998), only one gene (U55B) is HHV-7 specific, and there is no homologue to the HHV-6 U94 gene. It has been shown that HHV-7 gB attaches to CD4 molecules as a receptor (Lusso et al., 1994). It is likely that other molecules can act as receptors, and it is known that HHV-7 can infect cells that do not express CD4, e.g. lymphocytes, monocytes, epithelial cells, and fibroblasts. CD4 alone is not sufficient for a productive infection (Kempf et al., 1998). HHV-7 also establishes latent infection in CD4+ lymphocytes and macrophages, persistent infection occurs in salivary gland tissues as well, as shown by specific PCR (Sada et al., 1996). *In vitro*, only the CD4+ immature T cell line (SupT1) supports HHV-7 growth (Ablashi et al., 1998a). Due to CD4 affinity, HHV-7 competes for the shared receptor with HIV-1 (Lisco et al., 2007). Blockade of the CD4 molecule with anti-CD4 monoclonal antibodies (mAbs) or HIV-1 gp120 (which bind to CD4), inhibits HHV-7 infection of T cells. Exposure of terminally differentiated CD4+ macrophages derived from peripheral blood monocytes to intact or UV-inactivated HHV-7 prior to HIV-1 infection reduced the average level of HIV-1 p24 antigen production in cell culture supernatants by 91%, indicating that the mechanism of interference depends directly on the competition for CD4. It was suggested that this antagonistic effect be exploited to devise therapeutic approaches to AIDS. However, in prospective *in vivo* studies, HHV-7 was
detected in only 3% of HIV-1 infected patients and 12% of controls. It was suggested that this low level of detection resulted from HIV-1 out-competing HHV-7 for infection of CD4+ cells. There was no association between HHV-7 viral load in PBL and progression of HIV-1 disease (Crowley et al., 1996). HHV-7 has a strong down-regulation on CD4 mRNA and transcriptional activity in cord blood lymphocytes and SupT1 cell (Furukawa et al., 1994). The HHV-7 U21 open reading frame codes for an immunoevasin that inhibits the transport of class I MHC and CD4 molecules to the surface, thus infected cells are more difficulty recognizable by CD8+ cytotoxic T lymphocytes (Hudson et al., 2003). Expression of Kaposi’s sarcoma herpesvirus (HHV-8), K5 protein (MIR2) (Paulson et al., 2001) and adenovirus E3/19K protein (Lippé et al., 1991) also restrict surface expression of MHC class I molecules. HIV Nef polypeptide down-regulates both MHC class I and CD4 molecules (Mangasarian et al., 1999). In patients carrying several viruses simultaneously, the concerted action of HIV Nef and immunoevasins of heterologous viruses dramatically diminishes cytotoxic immune cell activism, resulting in the survival of virus-producing cells and consequently increasing bodily viral load. HHV-7 down-modulates CXCR4 surface molecule independently of CD4 in infected cells (Secchiero et al., 1998), which inhibit HIV-1 spread through the body. Differently than HHV-6A, HHV-7 does not down-regulate CD3, and has no effect on CD1, CD2, CD44 and CD49 T cell adhesion molecules (Yasukawa et al., 1993). HHV-7 down-modulates CXCR4 independently of CD4 in infected cells (Secchiero et al., 1998), which inhibit HIV-1 spread through the body. HHV-7 decreases CD38 levels, and slightly increases CD5 and CD57 on the surface of infected both SupT1 cells (Kirm et al., 1997). During the late stage of infection, HHV-7 increases the expression of CD46 at both the transcriptional and translational levels, as well as on the surface of SupT1 cells and primary CD4+ T cells. Together with CD59 overexpression, HHV-7 infected cells become more resistant to complement-dependent cytotoxicity than uninfected cells. CD46 overexpression facilitates infection of these immune cells by several heterologous viruses, among them HHV-6 and some adenovirus types, which are known to transactivate HIV-1 (Takemoto et al., 2007). Unlike with HHV-6, a generalized increase in host cell protein synthesis is observed in HHV-7 infected lymphocytes. Host genes whose expression is upregulated by HHV-7 infection include the lymphocyte specific G-protein coupled receptor EBI I, GADD45 (Kirm et al., 1997), GM-CSF and IL-15 (Atedzoé et al., 1997). Infection of PBMC’s obtained from seronegative individuals (mimicking primary infection) increases the level of intracellular mRNA and secreted polypeptides of TNF-α, TGF-β, IFN-γ, but decreases the production of IL-2 from mitogen (bacterial endotoxin polysaccharide, LPS and OKT3 mAb) activated PBMC. On the other hand, HHV-7 does not affect IL-4 and IL-6 synthesis (Atedzoé et al., 1999). In PBMC’s of seropositive persons (mimicking secondary infection), HHV-7 infection results in diminished IL-2 and IFN-γ production with or without mitogen activation. HHV-7 induces early IL-10 production, which is known to inhibit cytokine release from CD4+ helper lymphocytes. After a primary infection, HHV-7 causes significant inhibition of lymphocyte proliferation and overall the cellular immununity, but in repeated infections the overall effect of HHV-7 on cytokine production by infected cells is balanced. This might contribute to the moderate immunosuppression upon reactivation (Ongrádi et al., 1999a). HHV-7 also encodes two functional chemokine receptors, U12 and U51, which are counterparts of human CCR4 and CCR7. And whose natural ligands are CCL22 and CCL19, respectively. These receptors are expressed on T and B lymphocytes, and promote their translocation from the blood to the lymph nodes. Overexpression of these receptors facilitate the dissemination of infected lymphocytes throughout the body (Tadagaki et al., 2007).
HHV-7 is ubiquitous worldwide. Approximately 70% of children are infected and seroconvert before 4 years of age, usually following HHV-6B infection, but 30% of the population acquire infection later in life. In children, HHV-7 can induce exanthema subitum directly or, through activation of HHV-6B, may induce febrile convulsions or hepatitis. HHV-7 is reactivated in some patients 4 to 6 weeks after liver, kidney, bone marrow or stem cell transplantation, and may exacerbate human cytomegalovirus (HCMV) induced immunosuppression. HHV-7 can also reactivate HHV-6B in vitro (Katsafanas et al., 1996). In seronegative adults, HHV-7 can induce pityriasis rosea (PR) as presence of infective viruses, viral DNA and rising antibody as is indicated by increasing levels of IFN-α and -γ in the serum (Drago et al., 1997; Vág et al., 2004a). Although rare, cases of PR have been described in patients with HIV-1 infection. Several types of papulosquamous disorders might occur also in AIDS patients (Duvic et al., 1991). The lack of herald patch typical of genuine HHV-7 induced PR supports proper differential diagnosis. Due to some common immune pathways of HHV-7 and HIV-1 (e.g. alteration of cytokine pattern in the skin), PR might be mimicked in AIDS patients (Sadick et al., 1990). Interaction of HHV-6B or HHV-7 with human parvovirus B19 induces papular-purpuric gloves-and-socks syndrome (PPGSS, Ongrádi et al., 2000a; Vág et al., 2004b). HHV-7 is transmitted via saliva (Wyatt & Frenkel, 1992) and breast milk (Fujusaki et al., 1998). HHV-7 has been detected at the same ratio, more frequently, at higher viral loads, or in decreased quantity in saliva from HIV+ individuals with clinical symptoms of immunodeficiency than from controls by PCR in different studies (Di Luca et al., 1995; Lucht et al., 1998; Gautheret-Dejean et al., 1997). There is no evidence for congenital infection, although 2.7% of cervical samples obtained from pregnant women during the third trimester are PCR positive (Hall et al., 2008). Viral DNA is sporadically detected in the urine of healthy individuals, and in 6.5% of the cellular fraction of urine samples from HIV-1 positive patients with low CD4+ cell count (Gautheret-Dejean et al., 1997), but no infectious virus has been obtained from cervical and urine samples simultaneously. The HHV-7 pp85 protein was detected in 9 of 32 HIV-associated cases and in one of 7 classic sporadic Kaposi’s sarcoma lesions, which was localized to the cytoplasm of CD4-CD68+ cells of the monocyte/macrophage lineage. Dually infected HHV-6B and HHV-7 CD4-CD68+ cells were detected in 9% of these lesions. The cytokine-rich environment of Kaposi’s sarcoma might activate HHV-7 and subsequently HHV-6B (Kempf et al., 1997). These data suggest that HHV-7 also interacts with different viruses, among them HHV-6B, but does not activate HIV-1 directly and does not activate HIV-1 through HHV-6A activation. On the other hand, its immunomodulatory effects can be additive to immune suppression induced by HIV-1 in vivo.

6. Animal models to study transactivation by heterologous viruses

6.1 Simian AIDS model

A major hindrance to elucidating the in vivo role played by HHV-6A in AIDS has been the lack of a reliable animal model system (Lusso et al., 2007). Although simian (SIV) and feline (FIV) immunodeficiency viruses in their natural hosts provide appropriate models, the lack of known counterparts of Roseolovirus isolates from these animals impedes studies on the effect of simultaneous infection in AIDS progression. Peripheral blood lymphocytes of adult chimpanzees, pig-tailed macaques (Macaca nemestrina) and African green monkeys were found as susceptible to HHV-6A (Lusso et al., 1990, 1994) and HHV-6B (Levy et al., 1990) infections as were human PBL’s. Although HHV-6A infected PBL cultures of chimpanzees
exhibited CPE similar to that seen in human PBL and produced infectious virus (Lusso et al., 1990), this model is practically unavailable. The availability of pig-tailed macaques whose T cells are highly susceptible to HHV-6A infection is an ideal experimental model (Lusso et al., 1994). It has been established that in vivo coinfection with HHV-6A accelerates the course of SIV disease in pig-tailed macaques (Lusso et al., 2007). Three groups of young adult animals were infected by intravenous inoculation with either SIVsmE660 alone, HHV-6AGS alone, or both SIV and HHV-6A. Dually infected animals were first inoculated with SIV and then superinfected with HHV-6A 14 days later. None of the animals had detectable antibodies to HHV-6A and SIV before inoculation. Animals were observed for 32 months. HHV-6A infected animals developed clinical manifestations of mild to moderate intensity such as fever, splenomegaly, and generalized lymphadenopathy. Anti-HHV-6A seroconversion appeared after a mean of 3±1.4 and 2.2±0.5 weeks in HHV-6A and dually infected animals, respectively. SIV infection resulted in plasma viremia, and SIVp27Gag antigenemia at two weeks post-inoculation in both groups. Clinical signs included fever, generalized lymphadenopathy and splenomegaly, while the fever was higher and longer in duration in animals coinfe cted with SIV and HHV-6A. A transient loss of circulating CD4+ T lymphocytes was detected in singly and coinfected macaques. During the follow-up, no long term clinical or hematological alterations were seen in animals singly infected with HHV-6A, and their CD4+ and CD8+ T cell counts remained stably with the normal range. By contrast, a progressive loss of circulating CD4+ and CD8+ T cells was seen in coinfected animals. SIV superinfection of animals carrying HHV-6B for 13 to 21 months resulted in a very rapid decline of CD4+ and CD8+ T cells, and these animals developed AIDS-related conditions after 69 and 15 weeks of SIV superinfection (Lusso et al., 2007). Interestingly, the longer the duration of HHV-6A latency was, the shorter of AIDS-related conditions developed. This means that even latent HHV-6A infection induces irreversible changes in the immune system. Unlike the immunological parameters, the levels of SIV plasma viremia and antigenemia during the follow up were not significantly different between singly or dually infected macaques. Interestingly, disease progression in dually infected animals was accompanied by frequent episodes of HHV-6A reactivation, suggesting that SIV infection exerted a boosting effect on HHV-6A replication. Dually infected animals also showed a significantly expedited decrease in anti-HHV-6A antibody reactivity over time demonstrating exhaustion of humoral immunity. Lymph node biopsy one month post-inoculation showed follicular hyperplasia in all animals. However, in macaques singly infected with SIV or HHV-6A the nodal architecture was conserved, whereas in dually infected monkeys it exhibited a florid follicular hyperplasia with confluent germinal centers. Coinfected lymph nodes showed higher levels of SIV RNA deposited on the surface of follicular dendritic cells and HHV-6A mRNA expression in the extrafollicular area. Thus, HHV-6A and SIV could simultaneously replicate in coinfected lymph nodes. In biopsies obtained 6 months after inoculation, lymph nodes of dually infected animals showed significant atrophy of germinal centers. During the 32 months of the study, AIDS-defining clinical conditions developed in all coinfected macaques, but in only one of 4 infected with SIV.

It was also shown that reisolated SIV obtained from HHV-6A coinfected macaques after one year of infection had acquired resistance to RANTES (regulated upon activation normal T cell expressed and secreted). RANTES is a CCR5 binding chemokine that blocks the entry of SIV into cells, since SIV depends on CCR5 for infection. As has been previously discussed, HHV-6A is a potent RANTES inducer in lymphoid tissue (Grivel et al., 2001). In HHV-6A
HIV-Host Interactions

274

coinfected macaques, SIV subsequently evolved toward RANTES resistance, most likely under the selective pressure of elevated RANTES levels. Resistance to RANTES is increasingly recognized as a key virulence factor in HIV infection (Grivel et al., 2003), which may allow the virus to replicate in the high-RANTES milieu. One of the possible mechanisms whereby HHV-6A may foster the progression to AIDS is by facilitating an early acquisition of RANTES resistance (Lusso et al., 2007). In a recent study, SIV were reisolated from singly and HHV-6A-coinfected macaques. Surgically removed human tonsils in the presence of RANTES and PBMC from randomly selected healthy donors or from a homozygous CCR5-Δ32 +/+ donor were infected with SIV reisolates. All SIV isolates were able to replicate in human lymphoid tissue. Inoculation of different cell lines expressing several coreceptors (CCR2b, CCR3, CCR4, CCR6, CCR8, CXCR1, and CXCR4) were not able to support SIV infection. The majority of SIV isolates from HHV-6A coinfected macaques were not able to replicate in CCR5-Δ32 +/- PBMC’s showing that SIV variants, despite maintaining exclusive CCR5 coreceptor sensitivity, become resistant to HHV-6A and RANTES receptor competition. Cytokine polypeptide production in PBMC’s obtained from healthy donors was induced by infection using either SIV from singly infected animals or SIV from HHV-6 coinfectected animals. IL-2 production was significantly down-regulated while IFN-γ production was significantly upregulated in cultures infected with SIV derived from coinfected macaques as compared to the cytokine-inducing ability of SIV obtained after a single infection. For other Th1 and Th2 cytokines (IL-1α and -β, IL-4, IL-7, IL-12, IL-15, IL-16, and TNF-α), chemokines (MIP-1α and -β), other mediators (GM-CSF, IP10, MIG, and SDF-1β) no significant differences between lymphoid tissue infected with the two groups of SIV isolates were recorded. These results also indicate that SIV isolates obtained from HHV-6A-coinfected animals undergo a biological evolution in vivo, with the emergence of viral strains containing a reduced sensitivity to RANTES-mediated inhibition, thus, bypassing an important mechanism of virus control. It has been learned from clinical studies, that progression toward full-blown AIDS is often associated with the evolution of HIV-1 toward increased virulence. HIV-1 acquires the ability to use CXCR4 as a coreceptor, becoming resistant to the inhibitory effects of endogenous CCR5-binding chemokines. This phenotypic switch is typically accompanied by an accelerated loss of CD4+ T cells and suppression of Th1 polarized responses that play an essential role in the clearance of viral infections. These results are conclusive in vivo evidence that HHV-6A accelerates the progression of SIV toward full-blown AIDS (Biancotto et al., 2009), and excellently support human clinical and experimental data on the interaction of HHV-6A and HIV-1.

6.2 Feline AIDS as an ideal small animal model to study the interaction between retroviruses and different heterologous viruses

Although SIV infection is very close to the human analog monkeys are not available for the majority of research groups due to short supply and ethical considerations. Specific pathogen-free populations are nonexistent. Feline immunodeficiency virus (FIV), another member of the family Retroviridae has a pathogenesis similar to that of HIV infection, and because cats are both plentiful and available in specific pathogen free (SPF) status, they might prove to be an ideal model for AIDS cofactor studies. FIV shares many genetic, structural and biological characteristics with HIV. Although FIV shows tropism for CD4+ cells, its receptor is CD134 (Shimojima et al., 2004), and it requires further interaction with
chemokine coreceptors (CCR5 and CXCR4) for entry (de Parseval et al., 2006). RANTES inhibits FIV infection of feline PBMC’s, while antibodies against CXCR4, CCR5 and CCR3 reduce FIV infection. CD4+ and CD8+ T cells monocytes/macrophages are the major targets of FIV, in which it might establish latent infection. Upon virus activation, cells die of apoptosis (references in Bendinelli et al., 1995 and Burkhard & Dean, 2003). FIV diverges from other lentiviruses throughout the genome. Beside gag, pol, env and other small ORFs encoding regulatory proteins, the provirus contains two LTR elements, one at each end, which accommodate multiple regulatory elements. FIV LTRs appear to be strong basal promoters and poorly active in transactivation (Sparger et al., 1992). Regulatory sequences include one or two TATA boxes, and a variety of enhancer or promoter protein-binding sites (AP-1, NF-κB, etc). FIV transactivation is significantly different than that seen for HIV because FIV lacks TAT and the transactivating response (TAR) element (Sparger et al., 1992). Instead, FIV contains Orf-2 (also designated as Orf-A), a tat-like gene encoding a viral transactivator necessary for productive FIV replication in primary T lymphocytes as well as feline T cell lines (de Parseval & Elder, 1999). Unlike other lentiviral transactivators, FIV Orf-2 requires additional LTR elements for transactivation (Chatterji et al., 2002). Infection with FIV is usually associated with direct inoculation of the virus into the body via bites, and there is a distinct transient initial stage of infection that follows exposure by several weeks. After recovery from this initial disease, afflicted cats enter into a long asymptomatic stage of the infection that lasts for months or years before other signs appear. CD4+ T lymphocyte decline and inversion of the CD4/CD8 ratio are hallmarks of FIV infection, especially in neonates (Diehl et al., 1996) due to apoptosis induced by TNF-α overproduction (Ohno et al., 1993). Serum levels of IL-1, IL-6 and TNF-α increase in parallel with viral replication (Kraus et al., 1996). After in vitro treatment of separated PBMC in experimentally infected cats CD4+ lymphocytes produce TNF-α, IFN-γ, IL-2, IL-4 and IL-8, while CD8+ T lymphocytes express TNF-α, IFN-γ, and IL-2. Monocytes/macrophages are the source of IL-1, IL-6, TNF-α, IL-10 and IL-12p40 (Ritchey et al., 2001). The terminal AIDS stage of FIV infection is associated with a number of chronic common and opportunistic-type infections. Like HIV infection of humans, other infectious diseases may interact with FIV infection in the field to cause a more severe disease syndrome.

Retroviruses and herpesviruses are associated with a variety of diseases in animals. It has been suspected for a long time that their interaction may result in synergistic induction of diseases (Bacon et al., 1989). A possible interaction of feline herpesvirus type 1 (FHV-1, subfamily Alphaherpesvirinae) with FIV has been studied in vivo and in vitro. FHV-1 is a significant pathogen of family Felidae, causing an upper respiratory tract disease in cats. Dually infected animals it induces several immunological abnormalities (Reubel et al., 1992, 1994). FHV-1 also infects T lymphocytes. Productive coinfection of individual T lymphocytes has been detected (Kawaguchi et al., 1991). FHV-1 ICP4 was shown to modulate FIV LTR activity (Kawaguchi et al., 1994, 1995). Among other AIDS-promoting DNA viruses, adenoviruses (AdV) are known to cause fatal enteritis among terminal AIDS patients. The only feline adenovirus isolate (FeAdV) was obtained (Ongrádi, 1999) from a PCR positive fecal sample (Lakatos et al., 1997) of a cat with unknown FIV status. In Europe, 10 to 20% of free roaming cats are seropositive (Lakatos et al., 1996, 2000). FeAdV DNA has been detected in fecal samples of a child and her cat in Japan (Phan et al., 2006), and in a Brazilian child with upper respiratory tract infection (Luiz et al., 2010). Sequences of its hexon (Pring-Akerblom & Ongrádi, GenBank Accession No.
AY512566) and fiber (Pring-Akerblom & Ongrádi, GenBank Accession No. AY518270) suggest that FeAdV is related to human AdV type 1. It would be ideal to explore its interrelationship with both HIV and FIV, especially with respect to the role of AdVs in the intestinal complications of AIDS.

Another common interaction in nature is between FIV infection and feline leukemia virus (FeLV). About 10 to 15% of the cats clinically ill with FIV infection are coinfected with FeLV worldwide (Hosie et al., 1989; Ishida et al., 1989; Yamamoto et al., 1989). FeLV can also induce immunodeficiency (Rojkó & Olsen, 1984). In dually infected cats, the CD4+/CD8+ T lymphocyte ratio becomes rapidly inverted (Pedersen et al., 1990). FeLV induced tumors are a source of frequent and anticipated feline death (Shelton et al., 1990). This interrelationship is similar to what has been described for HIV and HTLV-I (Levy, 1993).

Besides viruses, other opportunistic infections can enhance the progression of feline AIDS. Both *Toxoplasma gondii* (Levy et al., 1998) and *Listeria monocytogenes* (Dean et al., 1998; Dean & Pedersen, 1998; Levy et al., 1998) disrupt the synergistic production of normal Th1 type cytokines, causing a loss of cellular immunity in FIV positive animals. These different systems clearly show that the progression of feline AIDS is facilitated by a wide array of microbes. Further studies are warranted to better delineate the role of other putative cofactors among the Roseoloviruses in FIV infection as an ideal small animal model for human AIDS.

### 7. Importance of rapid viral diagnosis, treatment and prevention of HIV-1 and HHV-6 simultaneous infections

Several transactivating herpesviruses cause severe, long-lasting, and unusual opportunistic infections in HIV-1 infected and AIDS patients. Heterologous viruses frequently show unusual resistance to antiviral drugs. The potential to transactivate HIV and cause opportunistic infection shows an intimate mutual relationship between these viruses and their relationship within the immune system. Prevention and suppression of both phenomena ought to be a continuous clinical task while treating and improving the quality of life of these patients.

There are excellent laboratory methods available to diagnose HIV-1 and 2 antibodies, and to determine the actual viral load in the serum of patients. Determination of their resistance to antiviral drugs is also routinely analyzed during treatment. Unfortunately, no serological tests are routinely available for the differential diagnosis of HHV-6 variants A and B. Immunofluorescent and ELISA methods determine the total quantity of anti-HHV-6 antibodies due to cross reactions, however the level of detectable serology can be insensitive when diagnosing immunocompromised populations. Several multiplex and real-time PCR assays are available for the simultaneous detection and quantification of HHV-6A, HHV-6B and HHV-7 specimens in patients (Safronet et al., 2003). Recently, the success of highly active antiretroviral therapy (HAART) in controlling HIV-induced immunosuppression has resulted in the disappearance of HHV-6 opportunistic infections, according to the trend already described for HCMV (Martinez et al., 2007; Salzberger et al., 2005). HHV-6 variants are sensitive to ganciclovir, foscarnet, cidofovir, IFN-α and IFN-β, and all of them have already been used in a small number of patients with different immunocompromised conditions. Some HHV-6A strains can carry mutations in the U69 gene responsible for phosphotransferase activity, consequently displaying resistance to treatment with ganciclovir (De Clercq & Naesens, 2006).
8. Future dimensions

Future research efforts could be directed toward hot topics such as the following:

First, it has not been established that cytokines and other mediators excreted from HHV-6 infected cells are structurally normal or have altered chemical structure (e.g., glycosylation, phosphorylation). It is also conceivable that HHV-6 carrier cells produce one or more unique soluble mediators that strongly transactivate HIV-1. Such aspects ought to be explored.

Second, results strongly suggest that persistent HHV-6 gene expression and replication sensitizes to HIV infection and rapid progression. Rapid progressors might carry integrated HHV-6, or may be progressing due to other potential yet presently unknown genetic immunological defects. Available samples of former and recent patients ought to be retested with this goal in mind. More attention must also be payed to these HIV-1 infected, HHV-6 carrier patients concerning anti-HHV-6 therapy. Gene therapy to suppress HHV-6 expression would be ideal to treat patients carrying integrated HHV-6.

Finally, further studies on the in vivo interrelationship between FIV and feline roseolovirus are necessary to understand the clinical aspects of dual infections of this nature. A feline counterpart of HHV-6 ought to be discovered and characterized.

9. Conclusions

HIV-1 infection is followed by a long disease-free period due to low transcriptional activity of the integrated provirus in resting CD4+ immune cells. Activation of CD4+ cells by mitogens, altered cytokine/chemokine milieu, or superinfection by heterologous viruses upregulate cellular, nuclear transcriptional factors, which in turn upregulate HIV-1 LTR directed gene expression by a tat-independent mechanism leading to augmented HIV-1 production. HHV-6 variant A possesses several alternative ways to upregulate HIV-1 infection and promote AIDS progression. Co-infection of HIV-1 carrier CD4+ cells results in enhanced cell death through apoptosis in vitro and in vivo, especially in the lymph nodes. Infection of immune cells leads to a shift in cytokine pattern from Th1 to Th2. Overproduction of TNF-α, IL-1 and IL-6 strongly transactivates HIV-1 via secondary messengers and the same nuclear transcriptional factors. Elevated levels of RANTES facilitate the change of CCR5-trop HIV-1 population towards the strongly cytopathic CXCR4 mutants. In the body, synergistic effects of immune evasion result in either a continuous or alternating presence of high level viremia, dissemination of the virus to all organs of the body which contributes to their failure and the consequentially premature death of AIDS patients. HHV-6A primarily damages cellular immunity, whereas HHV-6B predominantly suppresses the activity of humoral immune function. While HHV-6B infects CD+ immune cells, it hardly contributes to the activation of HIV-1, due to a differently modified cytokine/chemokine pattern. HHV-7 binds directly to CD4 molecules, therefore directly competing for this receptor with HIV-1. It is regarded as a harmless virus, but in successive stages of HIV-1 infection contributes to the gradual loss of CD4+ cells. There are molecular techniques for the simultaneous and rapid detection of these herpesviruses in vivo. Since the introduction of HAART, severe complications by HHV-6 have become rare, but if necessary ganciclovir and foscarnet can be used to inhibit these herpesviruses to improve the quality of life of HIV-1 infected patients.
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In Vitro and In Vivo Transactivation of HIV-1 by Human Herpesvirus 6


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In Vitro and In Vivo Transactivation of HIV-1 by Human Herpesvirus 6

295


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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and Trichomonas vaginalis on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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