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Molecular biology and clinical associations of Roseoloviruses human herpesvirus 6 and human herpesvirus 7

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SUMMARY

Human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) are members of the Roseolovirus genus within the Betaherpesvirinae subfamily. HHV-6 and HHV-7 primary infection occurs in early childhood and causes short febrile diseases, sometimes associated with cutaneous rash (exanthem subitum). Both HHV-6 and HHV-7 are highly prevalent in the healthy population, establish latency in macrophages and T-lymphocytes, are frequently shed in saliva of healthy donors, and the pathogenic potential of reactivated virus ranges from asymptomatic infection to severe diseases in transplant recipients. These features have contributed to the notion that HHV-6 and HHV-7 are more or less "harmless" viruses. Consequently, the medical and scientific interest originally prompted by their discovery has been gradually waning. The aim of this review is to provide a short update of the current knowledge on these viruses, and to suggest that the medical importance of Roseoloviruses should not be understimated.

KEY WORDS: HHV-6, HHV-7, Roseolovirus

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INTRODUCTION

Human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) have the typical morphologic characteristics of herpesviruses, including double stranded DNA genome, icosahedral capsid surrounded by a tegument, lipid envelope derived from infected cell membranes modified by the insertion of viral encoded glycoproteins (Figure 1). Complete viral particles have a diameter of 160-200 nm.

HHV-6 was first isolated in 1986 from cultured blood mononuclear cells of immunocompromised patients (Salahuddin *et al.*, 1986). Soon

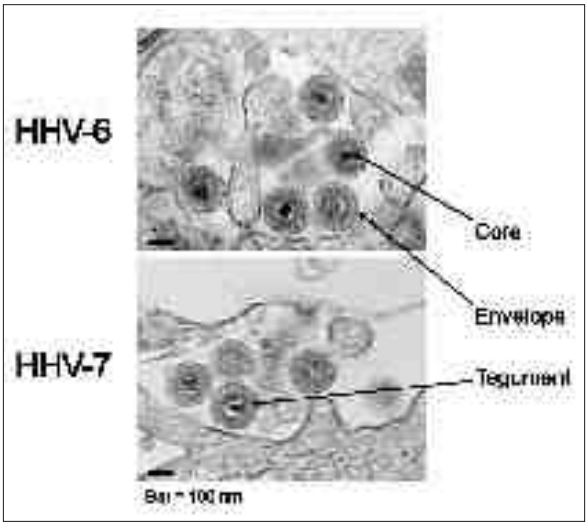

FIGURE 1 - *Electron microscope photograph of lymphoid cells infected with HHV-6 or HHV-7 The two viruses are morphologically indistinguishable. The capsid is enclosed by a prominent amorphous area (tegument) and surrounded by a glycoprotein envelope. Bar is 100 nm.*

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TABLE 1 - *Taxonomic structure of human viruses belonging to the Herpesviridae Family*

Subfamily	*Genus*	*Species*	*Common name*
Alphaherpesvirinae	Simplexvirus	Human herpesvirus 1 Human herpesvirus 2	Herpes simplex virus 1 Herpes simplex virus 2
	Varicellovirus	Human herpesvirus 3	Varicella-zostervirus
Betaherpesvirinae	Cytomegalovirus	Human herpesvirus 5	Cytomegalovirus
	Roseolovirus	Human herpesvirus 6 Human herpesvirus 7	- -
Gammaherpesvirinae	Lymphocriptovirus Rhadinovirus	Human herpesvirus 4 Human herpesvirus 8	Epstein-Barr virus Kaposi's sarcoma associated herpesvirus

afterwards it was determined that virus infection is common and that virtually all children are infected within the first few years of life. HHV-7 was isolated four years later from T lymphocytes of a healthy blood donor (Frenkel *et al*., 1990). Also HHV-7 infection is widespread in the human population, and infection is acquired during childhood (Wyatt *et al*., 1991). HHV-6 and HHV-7 share close genetic, biologic and immunologic features. This close relatedness is acknowledged by taxonomy and the two viruses are included in the Roseolovirus genus of the beta-herpesvirus subfamily (Table 1). Members of this genus are characterized by elective tropism for T lymphocytes, the ability to grow with less efficiency also in other cell types, high rates of latent infection in the human population, and by association with childhood febrile syndromes, which might be accompanied by rash. Furthermore, HHV-6 strains cluster in two distinct variants (HHV-6A, HHV-6B), which differ on the basis of distinct genetic, immunological and biological characteristics (Ablashi, 1991). Both HHV-6 and HHV-7 are highly prevalent in the healthy population, establish latency in macrophages and T-lymphocytes, are frequently shed in saliva of healthy donors, and their pathogenic potential ranges from frequent asymptomatic infection to rare cases of severe diseases in immunocompromised patients. These features have contributed to form the idea that HHV-6 and HHV-7 are more or less "harmless" viruses. Consequently, the medical and scientific interest originally prompted by their discovery has been gradually waning. The aim of this review is to provide a short update of the current knowledge on these viruses, and to suggest that the medical importance of Roseoloviruses should not be underestimated.

GENETIC CHARACTERISTICS

HHV-6. The viral DNA was completely sequenced in 1995 (Gompels *et al*., 1995). The genome is 160-162 kbp in size and is formed by a central unique region (approximately 143 kbp) bound at both ends by terminal direct repeats (each 8-9 kbp long). The direct repeats contain genetic elements that are necessary for viral DNA packaging and replication (Lindquester and Pellett, 1991) and include a tandem repetitive sequence that is also present in human telomers (Thomson *et al*., 1994). The genome of HHV-6B is predicted to contain 119 open reading frames (ORFs), 9 of which are absent in HHV-6A. ORFs encoded in the terminal direct repeats are identified with the prefix DR and those in the unique region are named U1-100, starting from the left end of the genome. Coding regions are located on both DNA strands, and a few genes are spliced after transcription. Overall, nucleotide sequence identity between HHV-A and HHV-6B is 90%, with variability according to specific regions. Some DNA regions are conserved between variants for over 95%, and other regions show higher divergence, with homology as low as 75% (Dominguez *et al*., 1999). Instead, variability within variants

is very low, and viral strain belonging to the same variant differ by 1% or less across their genomes (Pellett, 2001).

Several HHV-6 genes are conserved and present in the genome of all herpesviruses, and can be organized in seven gene blocks (Figure 1). One additional gene block comprises 17 genes conserved only in β-herpesviruses. There are also genes specific to Roseoloviruses, not present in the other herpesviruses, including U20-21, U23-24, U26, U85 and U100. Finally, two genes are unique to HHV-6 and present in both variants. One is U83, which encodes a chemokine with chemotactic activity for monocytic cells, and is expressed in two forms. The spliced variant is expressed as an early protein, before DNA replication, and the full length protein is expressed only after DNA replication (Dewin *et al*., 2006). The other gene unique to HHV-6 is U94, encoding a homologue of the human adeno-associated virus type 2 (AAV-2) rep gene (Thomson *et al*., 1991). The U94 gene product complements the replication of Rep-defective AAV-2 mutants, it localizes to the nucleus of the infected cell and it binds to the human TATA-binding protein, a transcription factor (Mori *et al*., 2000). It is transcribed under IE conditions and in latently infected lymphocytes (Rotola *et al*., 1999), suggesting that it likely contributes to the maintenance of latency. Recent results showed that U94 protein exogenously added to HHV-6 infected cell cultures strongly inhibits the replication of HHV-6 in *in vitro* infected cells (Caselli *et al*., 2006), confirming its regulatory function. Interestingly, although present only in the HHV-6 genome, U94 is able to inhibit the replication of all the beta-herpesviruses, including CMV and HHV-7 (Caselli *et al*., 2006).

HHV-7. The viral DNA was completely sequenced in 1996 (Nicholas, 1996), and the complete sequence was confirmed on a different viral strain two years later (Megaw *et al*., 1998). The HHV-7 genome is formed by a unique segment of 133 kbs flanked by direct repeated sequences (DR) that range in length from 6 to 10 kbp, so that genome length ranges between 145 and 153 kbp. Similarly to HHV-6, also HHV-7 genome contains herpesvirus conserved genes, arranged in gene blocks. The arrangement of conserved blocks 1 to 7 is identical between HHV-7 and HHV-6 (Figure 2), and amino acid sequence identity between HHV-6 and HHV-7 within the conserved genes is between 41% and 75%. Also HHV-7 encodes the genes typical of the Roseolovirus genus. Overall, 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.

In vitro growth properties

The replication cycle of Roseoloviruses lasts approximately 2-3 days in activated T lymphocytes grown in the presence of interleukin-2 (IL-2). The titer of infectious viral stocks obtained from infected cell cultures is low, ranging from 10^3 to 10^5 infectious units per ml. The cell type supporting higher levels of productive infection with HHV-6 and HHV-7 is represented by mononuclear cells obtained from umbilical cord blood.

HHV-6 and HHV-7 have a strict tropism for the human host, and it has not been possible to develop any animal model supporting viral infection,

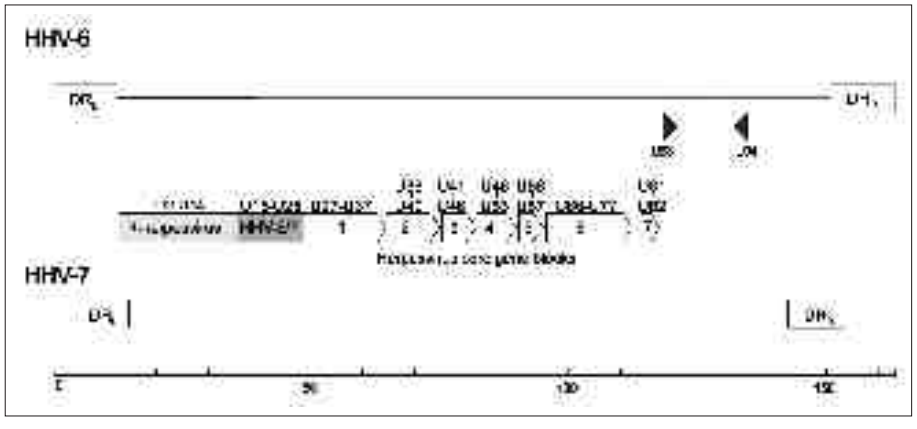

FIGURE 2 - *Schematic representation of HHV-6 and HHV-7 genomes, showing the direct repeats (DR), the positions of the seven conserved herpesvirus gene blocks, of the β-herpesvirus specific genes, and of the two HHV-6 specific genes (U83, U94).*

even if HHV-6 can grow in vitro in T lymphocytes from chimpanzees (Lusso *et al.*, 1990).

HHV-6. Originally, HHV-6 was named human B-lymphotropic virus (HBLV) (Salahuddin *et al.*, 1986), because it had been isolated from cultures of peripheral blood lymphocytes, but soon afterwards it was determined that the virus cell tropism is mainly directed to CD4 T lymphocytes (Lusso *et al.*, 1991, Takahashi *et al.*, 1989). Now it is known that HHV-6 is characterized by a broad tropism for different human cell types, and this observation is in accordance with the fact that the cellular receptor is the CD46 molecule (Santoro *et al.*, 1999), a ubiquitous type-1 glycoprotein member of a family of regulators of complement activation. However, only few cell lines expressing CD46 support efficient viral replication, suggesting that in addition to the presence of receptor, there is the need of specific requirements still unidentified. HHV-6A and -6B variants differ in the respective ability with which they can replicate in specific transformed T-lymphocyte cell lines. In addition, also CD8 T lymphocytes, γδ T lymphocytes and natural killer (NK) cells support HHV-6 replication (Lusso and Gallo, 1995, Lusso *et al.*, 1991, Lusso *et al.*, 1993). HHV-6 can also infect macrophages, dendritic cells, fibroblasts, epithelial cells and bone-marrow progenitors (Asada *et al.*, 1999, Kashanchi *et al.*, 1997, Luppi *et al.*, 1999, Robert *et al.*, 1996, Simmons *et al.*, 1992). Laboratory strains have been adapted to grow in specific human T cell lines, including Jurkat, JJHAN, HSB2 for HHV-6A, Molt-3, MT4 and SupT1 for HHV-6B (Black and Pellett, 1999), but the efficiency of viral replication is 1-2 fold lower than in primary cells.

Both variants are neurotropic and can infect neural cells, including astrocytes and oligodendrocytes, but HHV-6B supports only abortive infection, while HHV-6A establishes a productive infection that subsequently develops into latency (Ahlqvist *et al.*, 2005, Donati *et al.*, 2003).

HHV-6 can also infect endothelial cells, both *in vitro* and *in vivo* (Rotola *et al.*, 2000), establishing a low level productive infection (Caruso *et al.*, 2002). Both HHV-6A and HHV-6B can infect fibroblasts, but only HHV-6A produces low amounts of infectious progeny (Robert *et al.*, 1996). Therefore, the experimental evidence shows that HHV-6A and HHV-6B have differences in their cell tropism, and possibly HHV-6A is more virulent, but the reasons for this difference are still unknown.

HHV-7. HHV-7 was originally isolated from the peripheral blood lymphocytes of a healthy adult. The cells were activated with anti-CD3 monoclonal antibody (mAb) in conjunction with either IL-2 or anti-CD28 mAb (Frenkel *et al.*, 1990), and virus could not be isolated from unstimulated cells. It has been shown that HHV-7 uses CD4 as one of its receptors (Lusso *et al.*, 1994), but it is likely that other molecules can act as receptors, and the virus can infect also cells that do not express CD4 (Kempf *et al.*, 1998). Many different cell lines, including monocytes, macrophages, fibroblast, lymphocytes and epithelial cells, have been evaluated for their ability to support HHV-7 in vitro growth; only the CD4+ immature T-cell line SupT1 supports the replication of specific HHV-7 isolates (Ablashi *et al.*, 1998, Berneman *et al.*, 1992, Black *et al.*, 1997, Cermelli *et al.*, 1997). The ability to isolate HHV-7 from activated but not from resting PBL suggests that the virus may adopt a true state of latency in T-cells (Frenkel and Wyatt, 1992, Katsafanas *et al.*, 1996).

Effect on the host cell

Roseoloviruses infection causes significant alterations on the host cell metabolism. As is common with herpesviruses, infection induces shut off of host cell DNA synthesis (Katsafanas *et al.*, 1996), stimulates protein synthesis (Black *et al.*, 1992), and causes T lymphocytes to develop a cytopathic effect with characteristic ballooning, refractile and syncithial cells. Viral infection induces differential secretion of a wide array of cytokines and chemokines, including interferon-α, interleukin 1β, RANTES, tumor necrosis factor and many others (Caruso *et al.*, 2002, Flamand *et al.*, 1991, Inagi *et al.*, 1996, Kikuta *et al.*, 1990), depending on the virus and the cell type involved. HHV-6 infection upregulates CD4 in T lymphocytes and induces its expression in CD4-negative cells, while HHV-7 has a strong downregulation on CD4 (Furukawa *et al.*, 1994). HHV-6A, but not HHV-6B and HHV-7, downregulates CD3. HHV-6A and HHV-6B induced a general upregulation of T-cell adhesion markers (CD2, CD4, CD1, CD44, CD49), but HHV-7 had no effect on these molecules (Yasukawa *et al.*, 1993). Finally, both HHV-6 and HHV-7 suppress

the replication of CCR5-tropic human immunodeficiency virus (HIV), but show only mild inhibition of CXCR4-tropic HIV strains. Interestingly the viruses use different molecular mechanisms to induce the same effect: whereas HHV-6 affects HIV by upregulating RANTES (Grivel *et al*., 2001), HHV-7 suppresses HIV by downregulating CD4, the cellular receptor shared by HHV-7 and HIV (Lisco *et al*., 2007). Thus, each Roseolovirus has a different effect on cell biology.

Epidemiology

Both HHV-6 and HHV-7 are ubiquitous viruses and have a worldwide distribution. Seroprevalence is very high in the adult population, and specific IgG antibodies to HHV-6 and to HHV-7 are detected in more than 90% of adults. Primary infection occurs during early childhood. The peak for HHV-6 infection is observed at 6-9 months (Caserta, 2001), earlier than HHV-7, which occurs between 1 and 2 years of age (Wyatt and Frenkel, 1992). There are no convenient serological assays to discriminate between HHV-6 variants, however the available evidence suggests that the majority of clinical infections in immunocompetent patients are caused by HHV-6B. In fact, the viral sequences detected by PCR in latently infected healthy individuals belong almost invariably to HHV-6B (Di Luca *et al*., 1994, Di Luca *et al*., 1996)), supporting the notion that HHV-6A is less prevalent or that it establishes latency in different body districts, that are still undetermined. HHV-6A is detected more often in immunocompromised than in immunocompetent hosts, and appears to be potentially more neurotropic (Zerr, 2006).

The mode of transmission is unclear, but HHV-6 replicates in epithelial cells and is present in saliva, suggesting that oral secretions contribute to transmission, especially of HHV-6B (Clark, 2000, Levy *et al*., 1990, Simmons *et al*., 1992). Congenital infections occur approximately in 1% of births and are asymptomatic (Hall *et al*., 2004). Sequence analysis of HHV-6 isolated from mother/infant pairs suggests that mother-to-infant transmission can occur (van Loon *et al*., 1995), whereas there is no convincing evidence of sexual spread.

Also HHV-7 is transmitted most likely by the oral route, as infectious virus is continuously shed in saliva of healthy adults (Black *et al*., 1993, Wyatt and Frenkel, 1992). There is no evidence for HHV-7 congenital infection (Hall *et al*., 2004). However, HHV-7 DNA has been detected in the cellular fraction of 10.3% of breast milk samples collected from mothers between 2 and 24 days after delivery, suggesting the possible transmission by breast feeding (Fujisaki *et al*., 1998).

Latency

Like all herpesviruses, Roseoloviruses persist in the host following primary infection. Persistence may include both a true latent state, without production of infectious virus, and chronic replication with continuous or intermittent production of infectious progeny. Both forms of persistence develop in the same individual, with chronic infection taking place mostly in salivary glands (Di Luca *et al*., 1995a, Sada *et al*., 1996), while true latent infection, with episodes of reactivation, occurs mainly in macrophages and CD4+ T cells (Gompels *et al*., 1993, Kempf *et al*., 1997, Kondo *et al*., 1991, Miyake *et al*., 2006). PCR studies have shown that HHV-6 DNA sequences can also be detected in many different tissues from asymptomatic healthy individuals, including urinary tract, genital mucosa, fibroblasts and epithelium, thyroid, pancreas, liver (Chen and Hudnall, 2006, Di Luca *et al*., 1996), and HHV-7 DNA has been found in the gastric mucosa (Gonelli *et al*., 2001). However, there is no evidence that the virus can reactivate from these sites. The molecular mechanisms responsible for latency have been investigated only for HHV-6. It has been reported that latently infected cells contain four species of latency-associated transcripts, originating from the IE1/IE2 genic regions, with a transcription pattern similar to that of human cytomegalovirus (Kondo *et al*., 2002). Another transcript expressed during latent infection, in the absence of transcripts from lytic genes, is U94 (Rotola *et al*., 1998). Recently, we provided evidence that the U94 protein, exogenously produced and added to infected cell cultures, inhibits replication of all human beta-herpesviruses, including HHV-7 and HCMV (Caselli *et al*., 2006). HHV-6 can be reactivated in vitro from latency by infection with HHV-7 (Katsafanas *et al*., 1996), and immunosuppression plays an important role for in vivo reactivation.

The latency of HHV-7 is even less characterized. The molecular mechanisms have yet to be investigated, and experimental evidence shows that activation of infected T-cells results in the reactivation of HHV-7, but not of HHV-6 (Katsafanas *et al.*, 1996, Tanaka *et al.*, 2000).

Disease association

Roseoloviruses can be considered opportunistic pathogens which persist asymptomatically in immunocompetent individuals but can cause severe pathologies in the context of immunosuppression.

HHV-6. Primary HHV-6 infection in children causes exanthem subitum (ES) (roseola infantum, sixth disease) with high fever and the development of a rash after resolution of fever (Yamanishi *et al.*, 1988). However, only a subset (17%) of children with acute infection develop ES, and the majority suffer from undifferentiated short febrile illness, without appearance of rash (Hall *et al.*, 1994, Pruksananonda *et al.*, 1992). Although usually mild, ES may be accompanied by convulsions (Asano *et al.*, 1994, Hall *et al.*, 1994). Rare complications include hepatitis, arthritis, encephalopathy and haemophagocytosis syndrome (Hall *et al.*, 1994, Takagi *et al.*, 1996). Primary infection in older age groups is rare and results in an undifferentiated febrile illness or in an heterophile-negative infectious mononucleosis (Akashi *et al.*, 1993, Niederman *et al.*, 1988). Skin rash, hepatitis and atypical lymphocytosis may occur.

HHV-6 related diseases in adults are mostly the results of reactivation, which might be clinically significant especially in the immunocompromised host. HHV-6 can reactivate in immunocompetent individuals during pregnancy or periods of critical illness, requiring admission to intensive-care units (Dahl *et al.*, 1999, Razonable *et al.*, 2002). Many reports describe other possible disease associations involving HHV-6 reactivation (reviewed by De Bolle *et al.*, 2005).

In particular, the central nervous system is a potential target for HHV-6 pathogenesis. In fact, HHV-6 DNA is often detected also in autoptic brain tissue from healthy individuals (Chan, 2001, Cuomo, 2001), indicating that the virus is able to invade and persist asymptomatically in the CNS. The pathogenic potential of HHV-6 in the CNS is witnessed by several clinical reports (Kimberlin and Whitley, 1998). HHV-6 has been associated with neurological complications in children with primary infection (Suga *et al.*, 1993, Yoshikawa and Asano, 2000), encephalitis both in immunocompetent and immunocompromised patients (Drobyski *et al.*, 1994, McCullers *et al.*, 1995), demyelinating encephalomyelitis (Kamei *et al.*, 1997, Novoa *et al.*, 1997) and chronic myelopathy (Mackenzie *et al.*, 1995). HHV-6 DNA sequences are often detected in patients with temporal lobe epilepsy and the high levels of viral sequences suggest a potential etiological association (Donati *et al.*, 2003, Juntunen *et al.*, 2001, Uesugi *et al.*, 2000). Some reports suggest that HHV-6A may have higher neurotropism than HHV-6B (Caserta *et al.*, 1994, Cinque *et al.*, 1996, Wang *et al.*, 1999). For example, it was shown that HHV-6A has a considerably higher prevalence in cerebrospinal fluid than in peripheral blood mononuclear cells or in saliva of children (Hall *et al.*, 1998).

The difficulty with these studies is that HHV-6 infection is ubiquitous, it shows a wide tissue tropism, and therefore the detection of viral footprints in a pathological condition is not univocal proof of etiology. Viral presence might be due to latent virus, and viral reactivation may be a consequence, rather than the cause of disease. A further complication is the fact that there is not yet any biological explanation of how HHV-6 variants might differentially contribute to the pathogenesis. The proposed association of HHV-6 with multiple sclerosis (MS) is a paradigmatic example of how difficult it is to substantiate, or to disprove, HHV-6 etiological association. In 1995, Challoner *et al.* (Challoner *et al.*, 1995) proposed that HHV-6 might be associated with MS. One of the original observations was the presence of HHV-6 DNA sequences and antigens in the nuclei of oligodendrocytes from patients with MS adjacent to plaques of demyelination but not in control samples. The original report raised considerable interest, and subsequently, several studies were performed. However, after more than 12 years, the role of HHV-6 in MS is still controversial. Different groups reported contrasting results, even when similar techniques were used. For example, analysis by nested PCR of serum from MS patients yielded either positive or negative results (Goldberg *et al.*, 1999, Soldan *et al.*, 1997). In one study MS patients showed signif-

icantly elevated IgM responses to HHV-6 (Friedman *et al*., 1999), but in other reports the immunological reactivity (both IgM and IgG) in MS patients and controls was similar (Enbom *et al*., 1999). Active HHV-6 mRNA transcription in PBMCs of MS patients was reported in one study (Chapenko *et al*., 2003), but not in a previous report (Rotola *et al*., 1999). Interestingly, several pieces of evidence indicate that HHV-6A is more frequently involved in MS than HHV-6B (Ahlqvist *et al*., 2005, Alvarez-Lafuente *et al*., 2006, Rotola *et al*., 2004). However, other papers report negative findings (Mameli *et al*., 2007) and the association is far from proven.

There is substantial evidence that HHV-6 can be a significant pathogen in immunocompromised hosts. HHV-6 infection or reactivation in AIDS patients was reported to cause severe disease, such as fatal pneumonitis, encephalitis, retinitis and HHV-6 dissemination to many organs (reviewed by (Braun *et al*., 1997). Recently, the success of highly active antiretroviral therapy (HAART) in controlling HIV-induced immunosuppression resulted in the disappearance of HHV-6 opportunistic infections, according to the trend already described for HCMV (Salzberger *et al*., 2005).

HHV-6 is an important pathogen in organ transplant recipients (Dockrell and Paya, 2001, Singh, 2000, Singh and Carrigan, 1996). HHV-6 infection or reactivation occurs in nearly 50% of all bone marrow and in 20-30% of solid-organ transplant recipients, 2-3 weeks following the procedure (Dockrell and Paya, 2001, Yoshikawa, 2003). Prospective studies employing DNA detection by PCR or viral culture in sequential blood samples post-transplantation provide the strongest evidence for HHV-6 infection. The majority of HHV-6 infections post-transplantation are due to reactivation of HHV-6B, and the peak incidence of infection is 2-4 weeks post-transplantation (Griffiths *et al*., 2000, Singh and Carrigan, 1996). However, cases of primary infection due to transmission of the virus in donor tissue have been described, and superinfection with a donor strain distinct from the strain latent in the recipient may occur (Lau *et al*., 1998). Viral infection and/or reactivation may result in clinical symptoms, including fever (sometimes associated with leukopenia), skin rash, pneumonia, bone marrow suppression, encephalitis, and transplant failure (Carrigan *et al*., 1991, Cone *et al*., 1994, Drobyski *et al*., 1993, Griffiths *et al*., 2000, Zerr *et al*., 2001). Idiopathic bone marrow suppression is more common in bone marrow transplant or stem-cell transplant recipients, but can also occur following solid organ transplantation (Carrigan and Knox, 1994, Drobyski *et al*., 1993, Wang *et al*., 1996). Potential causes of marrow suppression include indirect effects mediated by cytokines and HHV-6 soluble products or direct infection of bone-marrow progenitors (Isomura *et al*., 1997, Knox and Carrigan, 1992, Luppi *et al*., 1999). HHV-6 infection is particularly associated with severe clinical symptoms in solid organ transplant recipients if concomitant HCMV infection occurs (DesJardin *et al*., 2001, Dockrell *et al*., 1997, Herbein *et al*., 1996). In spite of the available evidence that HHV-6 can be a serious pathogen responsible for complications in transplant recipients, definite proof is still under debate, mainly because the underlying pathophysiologic mechanisms have not yet been elucidated.

HHV-7. The spectrum of diseases associated with primary HHV-7 infection is similar to HHV-6, although usually clinical presentations are milder. HHV-7 infection is usually asymptomatic, but occasionally causes childhood febrile disease without rash (Cermelli *et al*., 1996) and exanthem subitum (Tanaka *et al*., 1994, Torigoe *et al*., 1995). Although relatively few cases of primary HHV-7 infection have been described, it is striking that many of them involve central nervous system manifestations, including hemiplegia (Torigoe *et al*., 1996, Torigoe *et al*., 1995) and febrile convulsions (Caserta *et al*., 1998, Clark *et al*., 1997, Torigoe *et al*., 1995). In one study, 75% (6 of 8) of children with primary HHV-7 infection developed seizures (Caserta *et al*., 1998). In addition, HHV-7 DNA was detected in the CSF of an epilepsy patient who was probably experiencing primary infection at the time (Portolani *et al*., 1998). Primary infections of adults are very rare, since virtually all individuals are infected by HHV-7 during early childhood. Nevertheless, primary HHV-7 infection in adults has been associated with encephalitis and flaccid paralysis (Ward *et al*., 1992).

Other clinical manifestations associated with primary HHV-7 infection include leukopenia, diarrhea, mild lymphadenopathy and sore throat

(Asano *et al*., 1995, Portolani *et al*., 1995, Torigoe *et al*., 1995). An association was proposed between HHV-7 and pityriasis rosea (PR), a relapsing skin disease associated with rash, which occurs during states of altered immunity (Drago *et al*., 1997a, Drago *et al*., 1997b) and subsequent studies confirmed a potential role of the virus (Broccolo *et al*., 2005). However this association is still uncertain, since other studies failed to confirm a role for HHV-7 in PR (Chuh *et al*., 2004, Yildirim *et al*., 2004). HHV-7 has also been associated with cases of hepatitis (Hashida *et al*., 1995), febrile syndrome (Portolani *et al*., 1995), symptoms mimicking chronic Epstein–Barr virus infection (Kawa-Ha *et al*., 1993) and mononucleosis in the absence of EBV (Chiu *et al*., 1998). Although higher HHV-7 antibody titres have been detected in patients with chronic fatigue syndrome (Sairenji *et al*., 1995, Secchiero *et al*., 1994), no differences were detected in the prevalence of HHV-7 DNA in PBL from patients and controls (Di Luca *et al*., 1995b), although the viral load was not measured.

As for HHV-6, a major problem in defining an association between reactivation of HHV-7 and specific diseases is represented by the difficulty of differentiating latent from active infection. Transcriptional analysis can be a useful tool to distinguish the mere presence of this ubiquitous virus from a true viral reactivation. Therefore, we developed this approach also for HHV-7 (Menegazzi *et al*., 1999) and used it in our studies. By this method, it was possible to investigate the potential role of HHV-7 in pathologic tissues harbouring viral DNA, such as gastritis (Gonelli *et al*., 2001) and periodontal disease (Cassai *et al*., 2003). In both cases transcriptional analysis revealed that HHV-7 was transcriptionally inactive inside infected cells, although viral DNA was present in the analyzed biopsies. These data therefore do not support an association between HHV-7 and chronic gastritis or destructive periodontal disease, and suggest that results based on the presence of viral sequences should be carefully interpreted in all cases of potential pathological associations.

There is only limited information on the role of HHV-7 infection in transplant recipients. It has been suggested that HHV-7 might have a role in delayed engraftment (Wang *et al*., 1996) and encephalitis (Chan *et al*., 2004), but the virus has not been definitely associated with any specific post-transplant clinical syndrome. One of the difficulties lies in the fact that HHV-7 can reactivate HHV-6 (Katsafanas *et al*., 1996), therefore the effects of HHV-6 might confound those of HHV-7.

Several studies have suggested that HHV-7 may be a possible cofactor for HCMV disease in organ-transplant recipients. HHV-7 DNA was detected in PBMCs of patients prior to onset of CMV disease in BMT patients (Chan *et al*., 1997) and similar results have been reported also for renal and liver transplantation (Kidd *et al*., 2000, Osman *et al*., 1996, Tong *et al*., 2000). Recently it has been reported that HHV-7 reactivation, together with HHV-6, might be important in pediatric stem cell transplantation (Savolainen *et al*., 2005). The picture is clearly complex and the ability to detect the exact timing of reactivation is critical. However, the results of these studies suggest that HHV-7 is active in some patients after transplant and that it might exacerbate disease associated with HCMV.

In patients immunosuppressed by HIV infection, the picture is still unclear. Since both HHV-7 and HIV-1 infect T-cells via the cell surface marker CD4, the interaction of these viruses within cells and during the course of AIDS has been investigated. *In vitro*, there was reciprocal interference between HHV-7 and HIV infection of PBL (Lusso *et al*., 1994). These data indicate that HHV-7 can inhibit HIV-1 infection in both phagocytes and lymphocytes *in vitro* and it was suggested that this antagonistic effect be exploited to devise therapeutic approaches to AIDS (Lisco *et al*., 2007, Lusso *et al*., 1994).

CONCLUSIONS

The field of research on Roseoloviruses is characterized by considerable uncertainty. Primary infection is often asymptomatic, the viruses are highly prevalent and their life-long persistency is not associated with medical problems. Therefore, the general perception, even among virologists, is that these ubiquitous agents are harmless and not a health threat. However, HHV-6 and HHV-7 can cause serious disease, mainly in immunodepressed patients, where viral reactivation plays important pathogenic roles which

possibly are still underestimated. Another aspect requiring more attention is neuropathogenesis in immunocompetent individuals, since these lymphotropic viruses have a significant tropism also for the central nervous system. Several problems are currently affecting the Roseolovirus field. One is the ability to discern which cases are really associated with the viral agent, ascertaining that these widespread viruses are not just bystanders. It is still unknown which viral footprints indicate a pathogenic role. Current debate focuses on whether the presence of virus in the plasma indicates a viremic state, or just a leakage of viral DNA from latently infected cells (Achour *et al*., 2006). Recent results show that HHV-6 DNA is integrated in the genome of almost 1% of blood donors (Leong *et al*., 2007), and therefore even detection of high viral loads is not an irrefutable hallmark of pathogenesis. Another problem is the existence of two HHV-6 variants, which although are closely related, differ remarkably concerning important features, such as genetic makeup, epidemiology, tissue tropism, pathogenic properties, and disease association. The scientific community has often discussed this issue, debating whether HHV-6A and HHV-6B should be considered different viruses, The discussion started over 15 years ago (Ablashi, 1991, Schirmer *et al*., 1991), but a general consensus has not yet been reached. The establishment of definitive disease associations is seriously hindered until the issue of differential pathogenic potential of variants is finally clarified.

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