Review

Human herpesvirus 8: an update

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Abstract

The discovery of human herpesvirus 8 (HHV-8) has opened a new field in the biology and in the clinical definition of HHV-8-associated diseases. Various aspects of the epidemiology, laboratory diagnosis and treatment of HHV-8 infection are still controversial. This review will summarise the most recent findings on the modalities of viral transmission in geographic areas where the virus is endemic as compared with those where the infection is sporadic. The studies on the interactions between HHV-8 and Epstein–Barr virus in the promotion of tumorigenesis will be then emphasised. This review will finally address the problems still open in the laboratory diagnosis and in the definition of antiviral drug susceptibility of HHV-8. Solving satisfactorily these issues will be necessary to better understand the epidemiology of HHV-8 infection, to reduce the risk of viral transmission, the progression of infected hosts to HHV-8-related malignancies and to achieve more active treatment options for these clinical conditions.

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1. Introduction

Human herpesvirus 8 (HHV-8) was discovered in 1994 by Chang et al. [1]. HHV-8 belongs to the γ-herpesvirus family and is the first known human member of the genus Rhadionovirus [2,3]. The use of classic epidemiology and laboratory techniques enabled scientists to associate this virus with Kaposi’s sarcoma (KS), multicentric Castleman’s disease and primary effusion lymphoma (PEL). In the last few years, detailed seroepidemiological and molecular studies have attempted to define how the virus is transmitted, as well as the gold standard among the laboratory tests used to define the viral infection, and the diseases associated with HHV-8 [4–8]. Furthermore, molecular biology studies focused on viral strategies to overcome host defences and to promote oncogenesis [9,10].

Despite these tremendous efforts, various aspects of the epidemiology, laboratory diagnosis and the nature of the diseases associated with HHV-8 infection need to be further defined. This review will summarise insights obtained in the most recent studies regarding the virology, epidemiology and the laboratory diagnosis and will discuss the controversial topics and the emerging hypotheses on HHV-8 infection.

2. The virus

HHV-8 possesses an icosahedral capsid surrounded by a lipid bilayer for a total size of 120–150 nm. The capsid is composed of four structural proteins; three of them (encoded by open reading frame (ORF) 25, 26, and 62) have significant sequence homologies to the capsid proteins of the alfa and beta herpesviruses, while ORF 65 lacks significant similarities [2,3]. The viral genome has been mapped and sequenced from genomic libraries from PEL cell lines and from KS biopsy specimens. It consists of a 140,5-bp-long unique coding region, encoding approximately 85 ORFs, including a number of homologues of cellular genes, flanked by an 800-bp non-coding tandemly repeated unit [9]. The HHV-8 DNA is circular during latent infection and linear during the lytic phase; viral replication occurs by the rolling circle mechanism within the nucleus of the infected cells. Among the viral genes expressed during latency, LANA 1 is present in nearly all infected cells and can be considered a universal marker of HHV-8 infection [2,11].

Among the viral genes expressed during latency, LANA 1 is present in the nucleus in nearly all infected cells and can be considered a universal marker of HHV-8 infection [2,11]. Among the viral genes expressed during the lytic replication, ORF K8.1 codes for two highly immunogenic proteins (gp K8.1A and K8.1B), ORF 26 codes for the minor capsidic protein and ORF 65 codes for the small viral capsidic protein [9,12,13]. Some of the products of the other viral genes are homologous to, and probably pirated from, known cellular genes; they are
of special importance because they counteract the host responses to viral infections by inhibiting the cellular immune response, the cytokine cascade and apoptosis [2,10].

Based on variation in ORF K1, six viral subtypes were identified (A, B, C, D, E and N), with more than 24 clades [14,15]; subtypes A and C predominate in Europe, subtype B predominates in Africa, while the distribution of the other rare subtypes is scattered in small geographical areas of Oceania and South America [4,7]. Recent findings showed that in apparently healthy Malawian people and in KS patients, intra-person sequence polymorphisms were observed in ORF 26, ORF 73 and ORF K1 HHV-8 genetic regions. Since K1 variation does not occur over the lifetime of a single infected host, these data may demonstrate that single individuals can be multiply infected by HHV-8, but it is not clear whether multiple viral carriage reflects co-infection with two or more strains, reactivation from latency or superinfection [16].

Productive herpesvirus infection leads to cellular lysis and is not consistent with the transforming ability of the virus; therefore the study of the viral cycle is essential to understand its pathogenic role. HHV-8 is able to infect several cell types and is usually present as nuclear episomal structures in a latent form (Table 1), while the lytic replication can take place in the peripheral blood, in tissues from KS and in Castleman’s disease, but generally occurs only in 5–10% of the infected cells [17]. In vivo and in vitro studies have demonstrated that HHV-8 can be latently maintained at undetectable levels in circulating B lymphocytes and monocytes, which may therefore serve as a reservoir for the virus. Furthermore, circulating monocytes may recruit the virus into tissues, and upon exposure to inflammatory cytokines, undergo lytic infection and transmit the virus to other cell types [18].

The presence of HHV-8 in KS lesions has been demonstrated in vessel endothelial and in spindle cells, where in situ hybridisation showed the expression of LANA-1, kaposin and viral cyclin D [4]. Compared with KS, a consistent proportion of PEL cells express viral IL-6 and viral IRF, suggesting the existence of two cell-type specific programmes of latency [8].

3. Modes of transmission and epidemiology

Despite a large number of epidemiological and virological studies, the exact modes of transmission of HHV-8 are yet to be fully elucidated [6,7]. Apart from the controversial findings, several data suggest that HHV-8 transmission modalities may differ between those countries where the virus is endemic and those where the infection is sporadic [7].

In the former, HHV-8 prevalence in children is very low before 2 years of age (after the disappearance of passively transferred maternal antibodies) and increases early after that age. These data suggest that HHV-8 is mainly transmitted among family members and close contacts by a horizontal, non-sexual route, while transmission during pregnancy and through breast-feeding has a minimal role in propagating the virus. In this situation, PCR in situ hybridisation demonstrated HHV-8 DNA in buccal and lingual epithelial cells, with the median log titre of HHV-8 in saliva ranging from 10^2 to 10^6 copies per ml. The same studies demonstrated that the concomitant viral load is consistently lower in the peripheral blood and in secretions from genital sites [8,19]; therefore, mucosal shedding data support direct contact with saliva as the most likely explanation for the viral infection [8,19,20].

In countries where the prevalence of HHV-8 infection is low, the situation is less clearly defined: in these settings, heterosexual transmission is probably not frequent, and this may be explained by the sporadic presence of low viral titres in vaginal secretions, in semen and prostatic tissues [21–23]. In contrast, many investigators agree that, among homosexual men, there is sexual transmission of the virus. Although the specific sexual activities resulting in HHV-8 infection have not been firmly established, infection may depend on sexual practices, which also include the transmission of oral fluids [7,19,23]. Among HIV-infected subjects, the independent association of HHV-8 infection with i.v. drug use suggested that HHV-8 is transmitted through needle-sharing. However, i.v. drug abusers and haemophiliacs have the lowest frequency of HHV-8 infection among HIV+ individuals, suggesting that the virus is infrequently transmissible via exposure to blood or blood products [2,6,7].

Although HHV-8 was discovered as a consequence of the tremendous increase in KS among HIV-positive individuals, it is an old virus that was present in Europe before the AIDS epidemic, probably since the earliest days of Homo sapiens [2,4,5]. The distribution of HHV-8 infection is very different in various parts of the world, and its prevalence is roughly correlated with the incidence of KS. However, several biases may alter the possibility of calculating such a correlation exactly, and the discrepancies observed between HHV-8 seroprevalence and KS distribution are probably due to under-diagnosis or underreporting of KS in areas with lower socio-economic conditions or from the different performances of laboratory methods used to detect HHV-8 infection [7]. It must be kept in mind that the epidemiology of HHV-8 infection is based on serological data, but it is widely recognised that the performance of the various antibody assays and the interpretation of the analytical results still differ, resulting in misclassification of HHV-8 data. Taking into account these limitations, the lowest HHV-8 prevalence has been reported.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Latent infection</th>
<th>Lytic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal B lymphocytes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PEL B lymphocytes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Endothelial/spindle in KS</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral epithelia</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
in Northern Europe, in the USA, in Latin America and in Asia (between 0% and 5%). In southern Europe, HHV-8 prevalence is high in Italy, but marked regional variations are present, with an increasing gradient of HHV-8 infection proceeding from north (less than 10%) to south (more than 20%) [2,4,7].

Sub-Saharan Africa represents an area where HHV-8 infection is endemic and where KS is very frequent. Prevalence ranges from 22% in central Africa to 87% in the Republic of Congo and Botswana [24,25].

In HIV-infected individuals, the rate of HHV-8 infection corresponds to the occurrence of KS among HIV risk groups. In fact, prevalence is higher among homosexual males, lower among i.v. drug users and heterosexuals; the lowest prevalence of HHV-8 infection is observed in HIV-positive children.

4. HHV-8 primary infection and associated diseases

Primary infection has been documented in children from Egypt and Cameroon by PCR detection of the virus in oral specimens [26,27]. It was associated with non-specific symptoms, like fever, fatigue, maculopapular rash and, occasionally, lymphadenopathy; seroconversion occurred within 6 months. Few cases of primary infection associated with more severe disease and including fever, lymphadenopathy, splenomegaly, leukaemia and KS, have been documented in immunocompromised hosts [2,5,6].

Epidemiological, serological and molecular biology studies provide strong evidence that HHV-8 is the aetiologic agent in all forms of KS, in PEL and multicentric Castleman’s disease [28–30]. KS is the most common cancer in the HIV setting, but the introduction of HAART has substantially lowered the probability of developing the disease. In HIV-infected subjects and in transplant recipients, immunosuppression is a common background of disease development, but the peculiar expression of virus-encoded proteins in affected tissues suggests that the pathogenic role of HHV-8 may depend on different gene expression in each disease [31,32]. In contrast, information regarding the pathogenic factors and the risk associated with the development of KS in the healthy population harbouring the virus in low- and high-incidence areas is lacking at the moment. It will be important to determine whether socioeconomic conditions, genetic factors or concomitant infections may influence the development of HHV-8-associated diseases in immunocompetent hosts. Coluzzi et al. [33] formulated an interesting, although difficult to prove, hypothesis suggesting that the development of classic KS forms in southern Italy may be due to exposure of the population living in these settings to blood-sucking arthropods. Particular attention has been devoted to studying the relationship between HHV-8 and multiple myeloma. Initial molecular biology studies demonstrated the presence of the virus in non-malignant adherent cells from cultures of bone marrow from myeloma patients [34], but subsequent studies did not confirm these findings [35,36]. To evaluate whether HHV-8 infection is associated with an increased myeloma risk, avoiding the possibility that the presence of myeloma disease might affect measurements, we performed a prospective study in a cohort of 40,000 healthy individuals, who were followed up to 23 years [37]. We did not detect an increased risk of myeloma associated with HHV-8 infection, but the statistical power of the study was low; therefore, a more extended seroepidemiological study using biobank specimens is under development. An active HHV-8 infection may also be associated with non-malignant illnesses, including fever and cutaneous rash after peripheral stem-cell transplantation, skin diseases and sarcoidosis. Cool et al. [38] very recently reported the presence of HHV-8 in the lungs of patients with primary pulmonary hypertension. These results, although they need to be confirmed, open a new scenario regarding a hypothetical pathogenic role of HHV-8 in selected, non-malignant, vascular disorders.

5. In vitro and in vivo drug sensitivity

Clinical reports have demonstrated that antiretroviral therapy containing protease inhibitors produces a positive clinical response in KS patients and a reduction in HHV-8 viraemia [39]. These HIV-unrelated effects of protease inhibitors are due to the impairment of cell invasion and of matrix metalloprotease activity, leading to control of angiogenesis, tumour growth and invasion, and promoting cell survival and tissue remodelling [40]. The possibility of efficiently treating HHV-8-associated diseases with novel therapeutic regimens prompted the setting-up of techniques to assess in vitro sensitivity to antiviral drugs. These assays demonstrated that HHV-8 was sensitive to cidofovir and ganciclovir, while sensitivity to acyclovir was weak. Antiviral drugs did not inhibit episomal virus DNA synthesis, suggesting that no benefit can be expected from antiviral drugs in HHV-8-positive lymphomas or during latency [41]; to clarify this issue, retrospective studies are ongoing to evaluate the in vivo activity of antiretroviral drugs and of antitumour chemotherapy on HHV-8 viral load in HIV+ patients with PEL and the possible correlations with disease status, HIV viral burden and CD4 counts (Simonelli and De Paoli, manuscript in preparation).

6. Laboratory diagnosis

The laboratory diagnosis of HHV-8 infection is based on serological and molecular biology assays to detect viral nucleic acids [2,4,7,42]. These tests are essential to study the epidemiology of this virus, for the clinical management of HIV-infected individuals and for organ transplantation, not only to screen organ donors, but also to assess the risk of KS after transplantation.
Serological assays are widely used to establish the prevalence of HHV-8 infection. Immunofluorescence assays using infected PEL cell lines were employed initially to detect anti-HHV-8 antibodies; in these cell lines, HHV-8 is mostly in the latent form, but lytic viral replication can be induced by tetradeacetyl phorbol acetate (TPA). The nuclear punctate fluorescence detected in uninduced PEL cells was the original marker of antibodies against the latent viral antigen LANA-1, and the cytoplasmic fluorescence detected in the TPA-induced cells was the marker of antibodies against HHV-8 lytic antigens [42,44]. In general, latent-antigen-based assays are less sensitive than lytic-antigen-based assays (80–90% vs. >95%, respectively) [4], and the appearance of lytic antibodies precedes that of latent antibodies [42,44]. However, the real specificity and sensitivity of lytic and latent antibodies are not completely understood, and the most widely used serological-testing algorithms include panels of antigens of both types [42,44–47]. Several immunoenzymatic tests and Western blots using purified or recombinant antigens have been established (Table 2). Initial studies comparing first-generation assays were disappointing, showing rather low concordance [48]; therefore, refinements in antigen preparation and purification procedures were soon attempted, and the use of alternative antigens in screening or confirmatory tests was investigated [49,50]. In order to reduce blood-borne viral transmission, the implementation of laboratory screening for HHV-8 infection is now considered a priority in laboratory medicine, but the lack of “reference” specimens representing true HHV-8-infected and non-infected individuals has prevented the evaluation of the performances of the various assays. To overcome this limitation, Pellett et al. [49] used a group of statistical methods known as “latent class” models. These statistical models enabled estimation of the sensitivity and specificity of several homemade HHV-8 antibody assays or algorithms performed by different laboratories and enabled the conclusion that all the laboratories participating in this study correctly identified all of the KS patient controls, but there was a limited area of disagreement when considering positivity among blood donors. The same study stated that the net performances of the assays and of the diagnostic algorithms of each participating laboratory were similar, making it difficult to declare any assay or algorithm clearly superior to the others. In conclusion, technical and interpretative HHV-8 serological issues have been greatly improved in the last few years, although a gold standard is still lacking.

Nucleic acid assays are essential tools in the diagnosis of and research on viral diseases, in particular when viral culture and identification are difficult to establish. It has been shown by these assays that HHV-8 is present in KS lesions, and this is an important diagnostic tool for pathologists [51,52]. To investigate the natural history of HHV-8 infection, qualitative molecular biology assays for the detection of the virus in different biological samples were initially developed [53,54]. Their sensitivity has been considered quite satisfactory, in the order of one to three genomic copies, but a major drawback of these assays is that the quality of the results depends on the application of stringent experimental conditions to avoid sample contamination leading to false positive results. Recommendations to overcome problems in amplification techniques include, (a) the routine screening for the presence of inhibitors of amplification; (b) the confirmation of positive results by a second amplification with alternative primer sets targeting another region; and (c) the separate processing of specimens with known or presumed high viral load [42,54]. Qualitative molecular assays using appropriate experimental conditions showed that, in infected individuals, HHV-8 is frequently detected in oral mucosal specimens, in plasma and in the peripheral blood mononuclear cells, while it is rarely found in the genitourinary tract [19,20,23]. In order to predict the progression of the infection and to monitor the efficacy of antiviral therapies, quantitative molecular assays have been developed recently [55,56]. Quantitative assays have a sensitivity of 10–100 copies [42,55,56], while in the absence of internationally recognised standards, their accuracy is still debated. Furthermore, the reproducibility of the entire HHV-8 quantification is still sub-optimal: we recently showed that the most critical steps are variations associated with DNA extraction and the preparation of samples, and that the coefficient of variability of the entire procedure was at best around 20% [55]. The clinical applications of quantitative molecular assays enabled

Table 2
Antigens and serological assays to detect anti-HHV-8 antibodies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name of the protein</th>
<th>Replication phase</th>
<th>Type of antigen</th>
<th>Assay</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORF 73</td>
<td>LANA</td>
<td>Latent</td>
<td>RP</td>
<td>WB</td>
<td>[28,44]</td>
</tr>
<tr>
<td>ORF 73</td>
<td>LANA</td>
<td>Latent</td>
<td>RP</td>
<td>ELISA</td>
<td>[45]</td>
</tr>
<tr>
<td>ORF 65</td>
<td>Small viral capsidic antigen</td>
<td>Lytic</td>
<td>RP</td>
<td>WB</td>
<td>[13,47]</td>
</tr>
<tr>
<td>ORF65</td>
<td>Small viral capsidic antigen</td>
<td>Lytic</td>
<td>RP</td>
<td>ELISA</td>
<td>[48]</td>
</tr>
<tr>
<td>ORF65</td>
<td>Small viral capsidic antigen</td>
<td>Lytic</td>
<td>PEP</td>
<td>ELISA</td>
<td>[42]</td>
</tr>
<tr>
<td>ORF 59</td>
<td>Processivity factor</td>
<td>Lytic</td>
<td>RP</td>
<td>ELISA</td>
<td>[32]</td>
</tr>
<tr>
<td>ORF 25</td>
<td>Major capsidic protein</td>
<td>Lytic</td>
<td>RP</td>
<td>ELISA</td>
<td>[46]</td>
</tr>
<tr>
<td>ORF 26</td>
<td>Minor capsidic protein</td>
<td>Lytic</td>
<td>RP</td>
<td>ELISA</td>
<td>[32]</td>
</tr>
<tr>
<td>ORF K12</td>
<td>Kaposin</td>
<td></td>
<td>RP</td>
<td>WB</td>
<td>[47]</td>
</tr>
<tr>
<td>ORF K12</td>
<td>Kaposin</td>
<td></td>
<td>RP</td>
<td>ELISA</td>
<td>[50]</td>
</tr>
<tr>
<td>ORF K8.1</td>
<td>Glycoprotein</td>
<td>Lytic</td>
<td>RP</td>
<td>ELISA</td>
<td>[47]</td>
</tr>
<tr>
<td>ORF K8.1</td>
<td>Glycoprotein</td>
<td>Lytic</td>
<td>PEP</td>
<td>ELISA</td>
<td>[50]</td>
</tr>
</tbody>
</table>
the definition of important biological and clinical aspects of HHV-8-associated diseases: (a) HHV-8 viraemia is elevated in KS and PEL patients before treatment; (b) although the detection of HHV-8 is feasible both in PBMCs and plasma, the latter contains a significantly higher number of viral copies; (c) HHV-8 load in peripheral blood is correlated with KS clinical stage [5,32]; and (d) there exists a correlation between the clinical response of KS patients to antiretroviral therapy and HHV-8 viral load, suggesting that this parameter may be very useful to assess the efficacy of different therapeutic regimens [5,39,42]. Unfortunately, DNA PCR cannot differentiate latent vs. lytic stage of the virus cycle and thus does not permit establishment of the in vivo viral activity in HHV-8-infected hosts and the study of the relative importance of cofactors that may eventually drive viral reactivation. In this context, an interesting prospective has been opened by experimental studies showing that Rta, a product of the ORF 50 gene that selectively transactivates viral promoters expressed during reactivation, is highly methylated in latent HHV-8 carriers, while it is unmethylated in patients with HHV-8-associated diseases [11]. A future area of investigation is the possible relationship among the presence of Rta demethylation, the reactivation of HHV-8 and the risk of developing associated diseases in HHV-8-infected individuals.

Molecular assays are also essential to study gene transcription in HHV-8-infected cells. A comparison of the HHV-8 gene expression profile in KS and in PEL showed that type 1B latency genes (LANA-2/vIRF-1) are transcribed only in HHV-8-associated B cell malignancies, while type II latency genes (K12 kaposin, vIRF-2) are transcribed only in KS [57,58]. The clinical application of experimental data describing HHV-8 transcriptional profiles is expected to provide important insights into the classification of HHV-8-associated diseases and into the selection of disease-targeted, drug-based or vaccine-based therapies.

7. PEL: a model to study interactions between HHV-8 and Epstein–Barr virus (EBV)

PEL is a rare lymphomatous tumour of body cavities that generally arises in HIV+ patients and, even more rarely, in the HIV-negative population. The PELs are of indeterminate immunophenotype, but the presence of immunoglobulin rearrangements enabled their classification as B-genotype. HHV-8 in PEL is present mostly in the latent state, although around 5–10% of PEL cells show evidence of lytic viral replication [2,10]. PEL development probably requires the accumulation of molecular lesions of cancer-related genes and the presence of multiple additional mechanisms, such as reduced immunocompetence, deregulation of cytokine synthesis, alteration in adhesion molecules and signal transduction abnormalities [10].

Several studies tried to clarify the mechanisms by which HHV-8 may exert its transforming ability. So far, multiple pathogenic pathways have been described, each contributing, for a still-undefined proportion, to the pathogenesis of PEL. After the infection of B lymphocytes, HHV-8 may replace c-myc activation as a step to the transformed phenotype and transactivate cellular genes involved in B cell activation, inducing the expression of CD23, a surface molecule closely associated with EBV-induced growth transformation, of CD25, the low-affinity IL-2 receptor and of CD38 [10]. LANA represses the transcriptional activity of p53, a tumour suppressor protein, while other HHV-8 gene products inhibit cellular apoptosis (vBCL2 and FLIP), regulate cell cycle (cyclin) and signal transduction (G-protein-coupled receptor). Concomitant viral infections represent additional factors in the pathogenesis of HHV-8-associated tumours. Experimental observations suggest a direct role of HIV-1, independently of its immunosuppressive effect, mediated through the ability of the HIV-1 Tat protein to trigger HHV-8 reactivation [59].

The presence of EBV in about 70–80% of PELs suggests an important role of this virus in the development of the lymphoma. EBV infection in PEL is mostly monoclonal and is characterised by the expression of EBNA-1, EBER and LMP2A [10]. The absence of major transforming proteins (vBCL2 and FLIP) has suggested that EBV is not singly responsible for PEL development. This issue has been recently addressed by an experimental protocol including the infection of HHV8+/EBV-negative PEL cell lines with the recombinant Akata cell-derived Neo EBV strain [60]. EBV-infected PEL cell lines were highly tumorigenic when injected into SCID mice, in contrast to their respective EBV-negative parental cells, but the precise mechanisms by which EBV exerts its activity have not been clearly understood.

Another pathogenic mechanism to promote PEL development may include a cross-regulation pathway between HHV-8 and EBV: both viruses are usually latent in the PEL cell lines, but they are inducible independently [17]. These experimental findings suggest that N-butyrate activation of HHV-8 expression shut off EBV lytic cycle gene expression, while EBV does not possess a reciprocal shut-off mechanism impairing HHV-8 expression, but the significance of these data is at the moment unknown. Further biological and clinical studies are now required to understand whether HHV8+/EBV-positive PEL have a specific pattern of viral replication, different prognosis or peculiar response to therapies compared with the HHV8+/EBV-negative counterpart (Simonelli et al., manuscript in preparation).

8. HHV-8 and organ transplantation

The incidence of KS after organ transplantation is 500–1000 times greater than in the general population, and this disease occurs in 0.5–5% of organ transplant recipients [61,62]. Transplant recipients who develop KS are usually infected with HHV-8 before transplantation, with a risk of developing KS estimated to be 8–37% and related to the
degree of immunosuppression [61–63]. Transplant recipients may also acquire the virus from HHV-8-infected donor organs; although the possibility that a proportion of neoplastic cells may originate from the spread of HHV-8 to recipient endothelial cells cannot be excluded, it has been shown in these patients that the HHV-8-infected neoplastic cells harboured the genetic or antigenic markers of their donors, thus demonstrating that the virus is transmitted through the transplanted organ [64]. Cost/benefit analysis of donor screening for HHV-8 infection before transplantation is lacking, but the identification of these individuals and a heightened surveillance for KS development in HHV-8-seropositive patients after transplantation are expected to become routine in the clinical setting.

9. Conclusions

HHV-8 is an ancient virus that was discovered recently, and many studies have addressed important findings in the biology, pathogenic factors and clinical conditions associated with its infection. Despite a tremendous amount of work on HHV-8, several issues remain to be elucidated.

In the absence of a gold standard, it is difficult to establish the analytical performances of serological assays, although the elaboration of diagnostic algorithms or the use of appropriate statistical methods may solve this problem. It is, therefore, conceivable that improvement in the positive predictive value of HHV-8 antibody detection methods will enable the safe screening of blood donations and the assessment of seroprevalence in populations at risk of developing KS, such as inhabitants of a part of the Mediterranean basin, HIV+ subjects and transplanted individuals. An important area of investigation is the possible correlation between reactivity to latent or lytic HHV-8 antigens and a latent or active HHV-8 replication, and the significance of these findings in various clinical situations.

While HHV-8 efficiently replicates in immunocompromised hosts, it is not clear whether the same situation occurs in the immunocompetent host. Pellett et al. [49] recently identified 138 American blood donors seropositive for HHV-8, but no viral DNA was detected in any of these donors, suggesting a possible, although not yet established, clearance of the virus after primary infection of immunocompetent hosts. Detailed investigations using molecular assays able to distinguish lytic from latent infection in different anatomical sites will be necessary to clarify this important issue. The connection between HHV-8 and diseases other than KS, PEL and Castleman’s disease has not been confirmed; it is conceivable that stringent application of the most recent serological and molecular biology techniques will be useful to clarify this issue in the near future.

The therapy of HHV-8-associated diseases has taken advantage of the concomitant activity against this virus of antivirals and protease inhibitors. However, treatment options could be greatly improved by establishing reliable in vitro and in vivo models for studying interactions between the drug and the virus itself and to obtain appropriate information on the pharmacokinetic and pharmacodynamic properties of novel anti-HHV-8 drugs.

It will be necessary to solve these issues satisfactorily to better understand the epidemiology of HHV-8 infection, to reduce the risk of viral transmission, the progression of infected hosts to HHV-8-related malignancies and to achieve more active treatment options for these clinical conditions.

References


