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Review

Human Herpesvirus 8
—Virology, Epidemiology and Related Diseases—

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CONTENTS:

SUMMARY: Human herpesvirus 8 ([HHV-8], Kaposi's sarcoma-associated herpesvirus [KSHV]) is a novel human oncovirus classified as a gamma-herpesvirus. HHV-8 is associated with Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and some cases of multicentric Castleman's disease (MCD). Antibodies against HHV-8 are detected in the sera of almost all KS patients, about 30% of HIV-infected homosexual males in the world and 1.4% of the Japanese population. In HHV-8-associated malignancies such as KS and PEL, HHV-8 latently infects these tumor cells. Unlike other viruses, HHV-8 encodes several human homologues including cytokines (IL-6, MIPs, IRFs) and regulatory proteins (cyclin D, G-protein coupled receptor [GPCR]). These proteins may play significant roles in the pathogenesis of HHV-8-associated diseases. It has been demonstrated in vitro that the functions of retinoblastoma and p53 proteins were inhibited by viral cyclin D and latency-associated nuclear antigen, respectively. Mice transgenic for GPCR have a KS-like region in the skin. These data suggest the full oncogenecity of HHV-8. On the other hand, many cells expressing lytic proteins are found in MCD tissues, suggesting that the pathogenesis of MCD is different from that of HHV-8-associated malignancies.

1. Introduction

In 1994, Chang et al. reported that two novel DNA fragments were discovered in Kaposi's sarcoma (KS) tissues (1). They used representational difference analysis (RDA), which is one of the subtraction PCR-based methods of purifying restriction-endonuclease-digested fragments present in one population of DNA fragments but not in others. Surgically removed specimens of KS and normal skin were investigated by means of the RDA, and the 330- and 631-nucleotide fragments were detected to be specific for KS (1). Since these sequences of the DNA fragments were found to be homologous with herpesvirus saimiri (HVS) and Epstein-Barr virus (EBV), they were considered as fragments of a novel human herpesvirus. Two years later, herpesvirus-like particles of this virus were found in lymphoma cells by electron microscopical analysis (2), and the virus was designated as Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8). The isolation of a new virus from KS tissues had a great impact on many scientists of various fields. Pathologists considered the association of virus infection with KS to be a significant finding that could explain the pathogenesis of malignant tumors. Since dermatologists had suspected an infectious viral origin of KS based on its clinical characteristics, they expected the effective management of KS using antiviral drugs. Molecular biologists who use gene subtraction methods considered RDA as a revolutionary method. Virologists considered the discovery of a novel human herpesvirus very important. Because both HVS and EBV are thought to be oncoviruses causing lymphomas in monkeys and humans, HHV-8 was presumed to be a new oncovirus. It has been shown that some HHV-8 encoded genes are homologous with oncogenes or cell cycle-associated genes. In this review, we summarize the virological and epidemiological aspects of HHV-8 infections, and HHV-8-associated diseases.

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2. Virology

2.1 Classification

HHV-8 is a new gamma herpesvirus classified as a member of *Rhadinovirus* (gamma-2 herpesvirus). In general, herpesviruses are classified into three subfamilies, i.e., alpha, beta and gamma. Herpes simplex virus-1, -2 and varicella-zoster virus (VZV) belong to the alpha subfamily, cytomegalovirus (CMV), HHV-6 and -7 to the beta subfamily, and EBV and HHV-8 to the gamma subfamily. The gamma herpesviruses are further classified into lymphocryptoviruses (gamma-1 herpesvirus) and rhadinoviruses (gamma-2 herpesvirus). While EBV is the prototype of lymphocryptoviruses, HHV-8 is a rhadinovirus, as are HVS, herpesvirus ateles (HVA) and rhesus rhadinovirus (RRV) (3). Sequencing analysis has revealed that HHV-8 is genetically similar to HVS. A recent study categorized rhadinoviruses into two, i.e., New- and Old-World gamma-2 herpesviruses (4). Although lymphocryptoviruses have been found only in Old World primates, rhadinoviruses have been found in both New-(HVA and HVS) and Old-(HHV-8 and RRV) World primates. Thus far, there is no report that HHV-8 was detected in monkeys, however, these genetic data suggest that HHV-8 may have originated from African monkeys (4).

2.2 Virion morphology

A complete viral particle of HHV-8 is 150 - 200 nm in diameter and consists of a capsid and an envelope (2, 5-8) similar to those of other human herpesviruses (Fig. 1A and 1B). In the nucleus, virus particles have a nucleocapsid (100 nm in diameter) without an envelope. The viral capsid contains a central DNA core, which appears to have a high electron density. The envelope is derived from the inner nuclear membrane, when viral particles bud into the cytoplasm from the nucleus. The tegument protein fills the space between the nucleocapsid and envelope. It is generally accepted that the features of viral particles are quite similar among herpesviruses, but related structures forming in the infected cells somehow depend on the type of virus. In comparison with other herpesviruses, the viral particle can be distinguished from that of CMV by electron microscopy; that is the tegument of CMV has a higher density than that of HHV-8, and CMV is accompanied by numerous dense bodies surrounding viral particles in the cytoplasm of infected cells which are not present in HHV-8-infected cells (6).

2.3 Genome structure and gene expression

The HHV-8 genome consists of a linear and double-stranded DNA about 170 kbp in length (9), which was sequenced almost completely within two years after its discovery (10). The HHV-8 genome consists of a long unique region (LUR) and a terminal repeat (TR) at both termini, which resembles the HVS structure (10) (Fig. 2). TR consists of an 801-bp direct repeat unit with 84.5% GC content. The number of repeats in TR may vary. The LUR is 140.5 kbp and has 53.5% GC content.

HHV-8 encodes more than 80 viral proteins on LUR (Fig. 2). The open reading frames (ORFs) are divided into two groups. The first group has a sequence homology to HVS and is designated as ORF-(number). The second group has no homology to HVS and is designated as K-(number). Kinetics of HHV-8-encoded genes was mainly investigated in HHV-8-infected primary effusion lymphoma cell lines stimulated with a phorbol ester such as 12-O-tetradecanoylphorbol-13-acetate (TPA) (11). Like other herpesviruses, the viral genes were categorized into lytic and latent genes and also into immediate-early (IE), early and late genes based on their expressions. The putative functions of HHV-8-encoded proteins are summarized in Table 1.

2.3.1 Immediate-early (IE) genes

Zhu et al. identified four cDNAs from HHV-8-infected cells by inducing viral reactivation in the presence of cycloheximide (CHX) and designated them as KIE-1 (encoding ORF50, K8 and K8.2), KIE-2 (encoding ORF45), KIE-3 (encoding K4.2, K4.1 and K4) and KIE-4 (unknown) (12). Among these, two IE proteins were extensively investigated. The first identified IE gene is ORF50 that is a homologue of *Rta*, a transcriptional activator encoded by EBV (11-14). Transcription of ORF50 results in its expression within 4 h after stimulation by TPA. This expression could not be

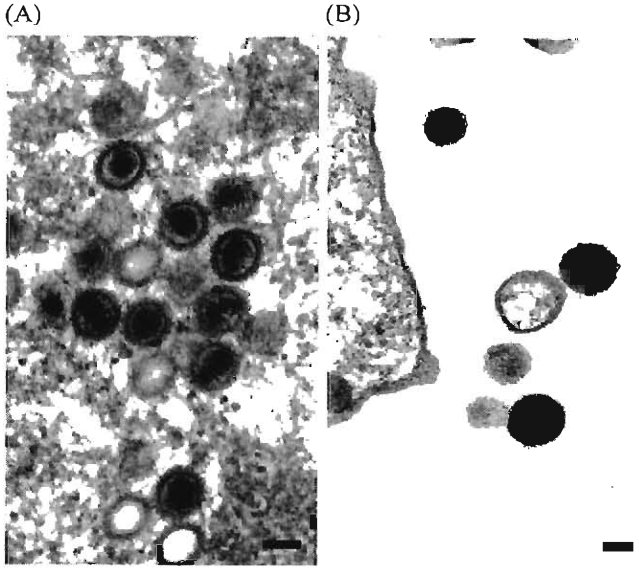

Fig. 1. Electronmicroscopy of HHV-8. Viral particles (virus capsids) in the nucleus (A) and cell surface (B) in the TPA-induced HHV-8-positive cell line TY-1. Bar = 100 nm. (Photograph by Ms. E. Moriishi)

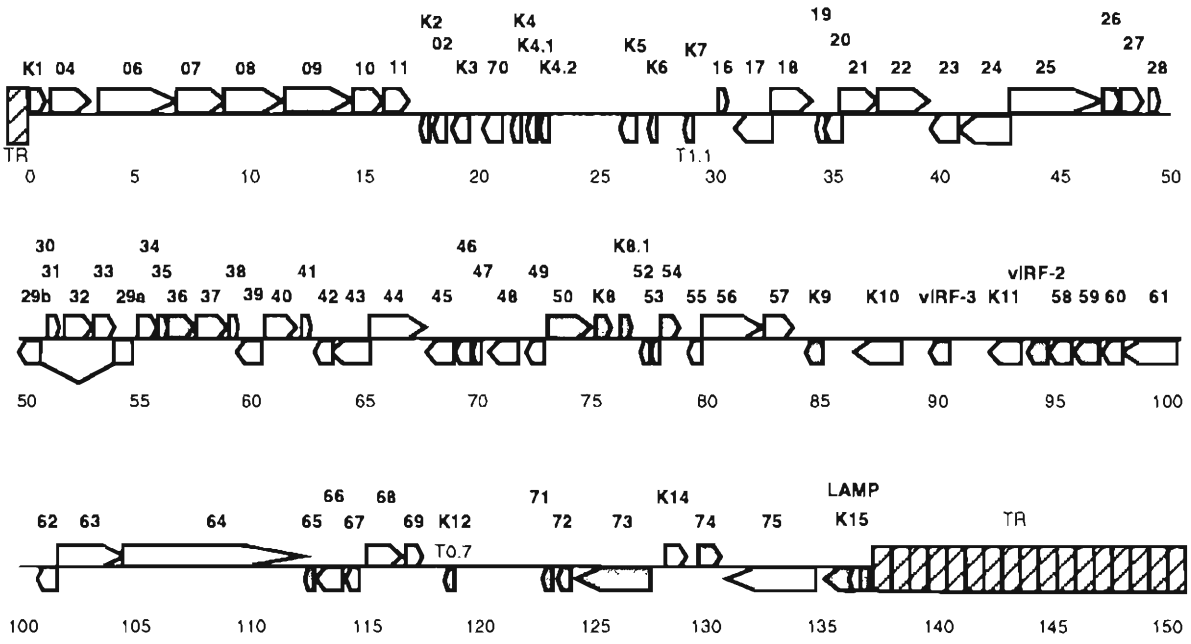

Fig. 2. Genomic map of HHV-8. ORFs are indicated by arrows. Gray arrows indicate that functions of ORF were reported (Refer to Table 1). TR=terminal repeat, vIRF=viral interferon regulatory factor, LAMP=latency-associated membrane protein.

blocked by phosphonoacetic acid ([PAA], a herpesvirus-DNA polymerase inhibitor) nor CHX (a protein synthesis inhibitor). Transfection of ORF50 to HHV-8-infected cells resulted in the activation of lytic gene expression (13). The transactivation was blocked by deletion of the C-terminal of ORF50. Interestingly, it was demonstrated that the C-terminal deletion mutant of ORF50 functioned as a dominant negative protein (13). Thus, ORF50 protein plays an essential role in the reactivation of latent HHV-8 in B cells. Another IE gene is K5 (15) whose expression is also unaffected by PAA and CHX, confirming its IE nature. The association of these two IE proteins is not the same as that of IE1 and IE2 of CMV (15). Transient-transfection assays showed that the K5 promoter was transactivated by ORF50 (15). In addition, the K5 protein is localized in the cytoplasm of induced and transfected cells (15). Thus, it is difficult to consider the functions of K5 solely from its localization and kinetics. Further studies are needed to clarify the function of K5.

2.3.2 Early genes

In herpesviruses, early genes are defined as genes whose expression is blocked by CHX but not by PAA. In gene expression studies, early genes encoded by HHV-8 were classified into two groups (11). The first group is expressed 8 - 13 h after chemical induction. K3, K8, K4 (vMIP-II), K2 (viral IL-6 [vIL-6]) and K7 (T1.1, PAN-RNA) are included in this group. The second group appears slightly later. This group includes ORF02 (vDHRF), ORF70 (thymidylate synthase), K6 (vMIP-I), ORF74 (viral G-protein coupled receptor [vGPCR]), K12 (T0.7), ORF16 (vBcl-2), ORF59 (processivity factor, PF-8) and ORF73 (latency-associated nuclear antigen [LANA])-lytic product. Generally, these early proteins, including DNA replication-associated enzymes, are associated with viral replication or optimization of microenvironments. Some of HHV-8-encoded cytokines or oncoproteins, including vIL-6 (K2), vMIPs and vIRFs, also belong to the early-late gene groups.

The K8 protein is a homodimerizing protein with a prototypic basic-leucine zipper (bZIP) domain at the C-terminal region (11,16,17). The amino acid sequence of K8 protein shows a significant homology to that of BZLF1, which plays a key role in the replication and reactivation of EBV. However, the functional data of K8 as a transcriptional activator have not yet been reported.

The K8.1 protein was cloned as an immunogenic glycoprotein (gp35-37) using patients' sera or the monoclonal antibody against HHV-8 (18,19). ORF-K8.1 was found to generate two spliced variants, K8.1A and K8.1B (19). These proteins were effectively reacted with human sera from HHV-8-infected individuals by Western blotting; thus, K8.1 may be a useful antigen for serological assays (18-21). Immunoelectron microscopy revealed that the K8.1 protein is localized on both cell and virion surfaces, suggesting that K8.1 is a virion-associated glycoprotein (20).

Nucleic acid replication proteins of HHV-8 are expressed in the early or late phase. ORF59 (PF-8) is a processivity factor of viral DNA polymerase encoded by ORF9 (22). ORF54 is also an early protein hydrolyzing dUTP to dUMP (23).

2.3.3 Late genes

Transcription of late genes is inhibited by PAA or CHX. More than 30 h is required for the transcripts to appear after chemical stimulation, and the maximum amount of transcripts is obtained 48 h afterwards. Genes encoding structural proteins belong to this category, e.g., ORF65 (a minor capsid protein) and ORF26 (also a capsid protein). ORF36, a serine-protein kinase, is also classified as a late protein (24).

2.3.4 Latent genes

A latency-associated gene cluster has been identified in HHV-8. This cluster includes K13 (ORF71), ORF72 and ORF73 genes, and is transcribed by two mRNAs (25). The ORF73 protein (LANA, LNA, or LNA-1) is expressed constitutively as a dot-like staining pattern in HHV-8-infected cells regardless of TPA stimulation (Fig. 4B). LANA and HHV-8 DNA have been shown to co-localize in the dots of interphase nuclei and mitotic chromosomes (26). This evidence suggests that LANA tethers HHV-8 DNA to chromosomes

Table 1. HHV-8 open reading frames (ORFs)

ORFs	Other Names	Kinetics	Function (Putative)	Other Information	References
K1			Deregulation of cell growth.	Membrane protein with immunoreceptor tyrosine-based activation motifs (ITAMs). Hypervariable region (+).	(77, 78, 124-131)
ORF4			(Complement binding protein)		
ORF6			(ssDNA binding protein)		
ORF7			(Transport protein)		
ORF8			(Glycoprotein)		
ORF9	Pol-8	Lytic	DNA polymerase	DNA synthesis activity (+). Binding to ORF59 (PF-8) which is a processivity factor of Pol-8	(22)
ORF10					
ORF11					
K2	vIL-6	E1	Homologue of human IL-6	Functional homologue of hIL-6. High expression in MCD.	(28-34, 58, 96, 102, 132-139)
ORF2		E2	(DHFR)		
K3		E1	Zinc finger membrane protein	Downregulation of MHC class I molecules. (HLA-A,B,C,D)	(36)
ORF70		E2	(Thymidylate synthase)		
K4	vMIP-2	E1	Homologue of human MIP-2	Angiogenic and HIV-inhibitory functions	(140, 141)
K4.1	vMIP-3	E1	Homologue of human MIP-3	Agonist for the cellular chemokine receptor CCR4	(35)
K4.2		IE			(12)
K5		IE	Zinc finger membrane protein	Downregulation of MHC class I molecules.(HLA-A and -B)	(11, 15, 36)
K6	vMIP-I	E2	Homologue of human MIP-1	Antagonist of CCR5. Inhibition of HIV replication. Angiogenesis.	(28, 137, 142, 143)
K7	T1.1, nut-1	E1	Lytic cycle associated polyadenylated nuclear RNA	Formation of ribonucleoprotein complexes	(144-146)
ORF16	vBcl-2	E2	Homologue of human Bcl-2	Inhibition of apoptosis.	(47, 147-149)
ORF17			(Capsid protein)		
ORF18					
ORF19			(Tegument protein)		
ORF20					
ORF21			(Thymidine kinase)		
ORF22			(Glycoprotein)		
ORF23					
ORF24					
ORF25			(Capsid protein)		
ORF26		Late	Capsid protein	Origin of KSBam330	(58, 150, 151)
ORF27					
ORF28					
ORF29b			(Packaging protein)		
ORF30					
ORF31					
ORF32					
ORF33					
ORF29a			(Packaging protein)		
ORF34					
ORF35					
ORF36		Late	Serine-protein kinase	Autophosphorylated serine-protein kinase	(24)
ORF37			(Alkaline exonuclease)		
ORF38					
ORF39			(Glycoprotein)		
ORF40			(Helicase-primase)		
ORF41			(Helicase-primase)		
ORF42					
ORF43			(Capsid protein)		
ORF44			(Helicase-primase)		
ORF45		IE	Immediate early transcript		(12)
ORF46			(Uracil DNA glucosidase)		
ORF47			(Glycoprotein)		
ORF48					
ORF49					
ORF50	Rta	IE	Transactivator	Immediate early gene of HHV-8.	(11-14, 152, 153)
K8	K-bZIP	E1	bZIP protein	Homologue of EBV BZLF1. Forming homodimer.	(16, 17)
K8.1	gp35-37	E	Virion glycoprotein	Immunogenic virion glycoprotein. Variant forms, A and B.	(18-20, 58, 69, 154-157)
K8.2					(12)

Table 1-Continued

ORFs	Other Names	Kinetics	Function (Putative)	Other Information	References
ORF52					
ORF53					
ORF54		E	dUTPase	Hydrolysing dUTP to dUMP	(23)
ORF55					
ORF56			(DNA replication protein)		
ORF57		E	Homologue of EBV M protein	Homologue of a transactivator of EBV	(13)
K9	vIRF-1	Lytic	Homologue of human IRF-1	Repression of transcriptional activation induced by IFNs. Transformation activity (+).	(28, 49-51, 158-163)
K10		Lytic			(58)
vIRF-2	vIRF-2	Lytic	Homologue of human IRF-2	Binding to the NF-kappa B binding site.Interaction with RelA (p65) and p300	(164)
K11		Lytic			(58)
vIRF-3	vIRF-3	Lytic	Homologue of human IRF-3		(164)
ORF58					
ORF59	PF-8	Early-Late	Processivity factor of Pol-8	Processivity factor of DNA polymerase (Pol-8). Immunogenic protein.	(22, 74, 157, 165)
ORF60			(Ribonucleotide reductase)		
ORF61			(Ribonucleotide reductase)		
ORF62			(Assembly/DNA maturation)		
ORF63			(Tegument protein)		
ORF64			(Tegument protein)		
ORF65	VCP	Late	Capsid protein	Immunogenic small capsid protein.	(21, 58, 166)
ORF66					
ORF67			(Tegument protein)		
ORF68			(Glycoprotein)		
ORF69					
K12	T0.7, kaposin	Latent? (E2?)		Transforming gene. Latency-associated.	(144, 146, 167-170)
K13	vFLIP ORF71	Latent	Homologue of human FLIP	Prevention of apoptosis induced by death receptors.	(48, 171-174)
ORF72	v-cyclinD	Latent	Homologue of human cyclin D1	Formation of cyclin-cdk6 complex which degradate p27(kip) cdk inhibitor.	(25, 39, 40, 148, 168, 174-186)
ORF73	LANA, LNA	Latent	Binding to chromosome	Tethering viral genome to host chromosome. Interaction with RING3. High expression in infected cells. Strong immunogen.	(21, 25-27, 41, 42, 57, 69, 174, 187-192)
K14			Homologue of human OX-2		(174)
ORF74	vGPCR	E2	Homologue of human GPCR	Oncogene. Angiogenesis activator. Formation of KS-like regions in transgenic mice.	(43-45, 148, 176, 193-203)
ORF75					(124, 150)
LAMP		Latent	Latency-associated membrane protein	Similar to LMP-1 and -2A of EBV. Interaction with TRAF1, -2, and -3.	(46)
K15				Demonstration of viral strain variability.	(131, 150, 204, 205)

*Gray columns indicate that the functions of ORFs were reported. This table was based on the table by Russo et al (10).

during mitosis which allows the segregation of HHV-8 episomes into progeny cells (26). The LANA protein associates with the p53 protein to inhibit the activity of p53, thereby preventing apoptosis of HHV-8-infected cells (27).

2.4 HHV-8-encoded cytokines and oncoproteins

A distinct feature of HHV-8 is that it encodes some homologues to human transforming or regulatory proteins and cellular cytokines in its genome. HHV-8-related diseases such as KS, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) have been believed to be associated with the cytokine network. It is probable that HHV-8 plays some role in the alteration of the cytokine network to optimize the microenvironment for cell growth using viral cytokines. In addition, viral cytokines are sometimes synergic with viral oncogenes. The relationship is complex and remains unclear to date.

2.4.1 Viral cytokines

Among viral cytokines encoded by HHV-8, K2 (vIL-6) is one of the most important proteins in the pathogenesis of HHV-8 related diseases. In particular, IL-6 is thought of as the key protein in the pathogenesis of KS. vIL-6 was shown to be functional by B9-cell proliferation assay (28) and to activate the signaling pathway of human IL-6 (hIL-6) (29). In addition, it was demonstrated that vIL-6 induces the expression of vascular endothelial cell growth factor (VEGF) resulting in neoangiogenesis (30). It is possible that vIL-6 contributes to the induction of hIL-6 in infected cells because of the high level of hIL-6 in the culture supernatant of HHV-8-infected PEL cell lines. On the other hand, recent studies demonstrated that vIL-6 signals were different from hIL-6 signals in vitro (31-34). These data suggest that vIL-6 plays an important role in the pathogenesis of KS; we, however, do not consider vIL-6 to be only an analogue of hIL-6.

HHV-8 encodes three types of MIPs, i.e., vMIP-I (K6), -2 (K4) and -3 (K4.1). These chemokine-homologues may induce angiogenesis and inhibit T cell responses (35). In addition, K3 and K5 also contribute to the suppression of the response of T cells by downregulating major histocompatibility complex (MHC) class I in HHV-8 infected cells (36).

2.4.2 Viral oncoproteins

The transformation activity of HHV-8 has been demonstrated by an infection experiment using endothelial cells (37, 38). Therefore, it is unequivocal that HHV-8 has transformation genes.

Viral-cyclin D (ORF72) inhibits the activity of retinoblastoma protein (Rb), which regulates the G1 phase to S phase of the cell cycle (39), whereas LANA can interact with the p53 protein and inhibit the transcriptional activity mediated by p53 (27). Both LANA and v-cyclin D are latent proteins which are expressed constitutively in HHV-8-infected cells such as KS spindle cells (40-42). Thus, HHV-8 encodes proteins regulating the activity of p53 and Rb, which are two key proteins in tumor-suppressor pathways.

vGPCR (ORF74) is another regulatory protein encoded by HHV-8 (43,44). Transfection of vGPCR to NIH3T3 cells resulted in the transformation, and inoculation of transfectants in severe combined-immunodeficiency (SCID) mice resulted in KS-like lesions at inoculation sites (44). Notably, spindle cells in the lesions strongly express VEGF, suggesting that vGPCR induced the expression of VEGF in the transfectant cells (44). KS-like lesions were also formed in the skin of vGPCR-transgenic mice (45). These data suggest that vGPCR plays a central role in the pathogenesis of KS.

Latency-associated membrane protein (LAMP) is another candidate for the HHV-8-encoded oncogene (46). LAMP is encoded in the genome region from ORF75 to TR, which contains the K15 gene. This protein has 12 transmembrane domains and is homologous to LMP2A of EBV. The full transformation activity and interaction with TRAF-1, -2 and -3 were reported (46).

Viral Bcl-2 and viral FLICE-inhibitory protein (vFLIP) were demonstrated to inhibit apoptosis (47,48). On the other hand, viral interferon regulatory factors (vIRFs) were shown to inhibit the interferon signaling pathway (49-51). However, it is noteworthy that these proteins are classified into the lytic class of viral proteins. Considering that most HHV-8-infected cells are in the latent phase, these lytic proteins can have no major role in the pathogenesis of HHV-8-associated malignancies.

2.5 Experimental infection in vitro

HHV-8 transmission was first reported using 293 cells (transformed human kidney cell line) but with a very low efficiency (52). Thus far, an efficient viral propagation system is not available except through the use of HHV-8-positive lymphoma cell lines in combination with chemical stimulation using TPA or *n*-butylate. The transmission of HHV-8 to endothelial cells has been investigated in vitro by several groups (37,38,53,54). Dermal microvascular endothelial cells (DMVECs) transfected with the human papillomavirus (HPV) E6 gene were effectively infected with HHV-8 by exposure to cell-free supernatants derived from TPA-treated BCBL-1, an HHV-8-infected PEL cell line (38). About 5% of HHV-8-infected DMVECs spontaneously expressed ORF59, a lytic protein of HHV-8, 8 weeks after infection, while LANA was expressed in 80% (38). HHV-8-infected DMVECs exhibited morphological changes and also displayed a transformation activity showing the loss of contact inhibition and growth in soft agar (38). Another group reported that highly concentrated viral particles derived from the supernatant of TPA-stimulated BCBL-1 is required for transmission of HHV-8 to other types of endothelial cells (54). Thus, HHV-8 can infect endothelial cells in vitro; however, cell-free transmission was employed in all these experiments. Because a previous report suggested that peripheral blood B cells play the role of a reservoir (55), cell-mediated (cell-to-cell) transmission may be predominant in vivo. Therefore, further studies using cell-mediated transmission are needed to clarify the HHV-8 transmission.

3. Diagnosis of HHV-8 infection

3.1 PCR

Since HHV-8 was discovered as DNA fragments from KS, Southern blot hybridization and PCR were first used for the detection of HHV-8 in KS tissues. The first-discovered $KSBam330_{233}$ region of HHV-8 (a 233-bp sequence in the 330-bp fragment, one of the *Bam*HI DNA fragments) was often employed as a target gene for PCR (1). PCR using these primers is highly sensitive and the HHV-8 genome has been detected in specimens from patients with various diseases including KS, sarcoidosis, MCD, body cavity-based lymphoma (BCBL) (or PEL), various skin lesions (e.g., squamous cell carcinoma, and seborrheic keratosis), and multiple myeloma. However, PCR results included obviously false-positive results. Today, evidence shows that HHV-8 infection is associated with only a limited number of diseases.

3.2 Histological detection of HHV-8

Histological detection of HHV-8 appears to be difficult. Because quantitative PCR revealed only a low copy number (nearly single copy) of HHV-8 in KS, an in situ PCR method was employed to detect the HHV-8 genome (56). However, its sensitivity and specificity were not sufficient to determine the precise localization of this virus. Today, the most sensitive and convenient histopathological method of detecting HHV-8 is immunohistochemistry using the antibody against the ORF73 protein (LANA), one of the latent proteins of HHV-8. Most KS or PEL cells are positive for the ORF73 antigen, suggesting that all these cells are latently infected with HHV-8 (Fig. 3,4) (41,42,57). Several antibodies against lytic antigens were developed, however, these antigens were rarely expressed in HHV-8-associated diseases (58). In situ hybridization to detect the T0.7 and T1.1 genes which are the latent and early genes of HHV-8, respectively, was also used, but the expression levels of these genes are low in KS lesions.

3.3 Serology

Anti-HHV-8-antibodies can be detected in the sera of HHV-8-infected individuals. The seroprevalence of HHV-8 has been found to vary between studies, depending on the type of assay employed and the countries where the investigations were carried out (59-67). To date, two methods, immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA), have been used to detect antibodies against HHV-8. However, the target antigens differ for each method. In IFA, LANA corresponding to the ORF73 protein is the major antigen; in ELISA, ORF59 (PF-8), ORF65 (a minor capsid protein), ORF26 (another possible minor capsid protein), ORF73 (LANA) or a lysate of whole viral particles have been used as antigens (60,61, 65-71). The use of these different antigens seems to have caused discrepancies in data reported so far (65). Recently, it was shown that lytic proteins such as ORF 65, K8.1A and K8.1B, and the latent ORF73 protein exhibited high reactivity with the sera of HHV-8-seropositive individuals as determined by Western blot analysis (21,69). Based on these results, ELISAs, using ORF59, ORF65, K8.1A, K8.1B and ORF73 antigens and with high detection

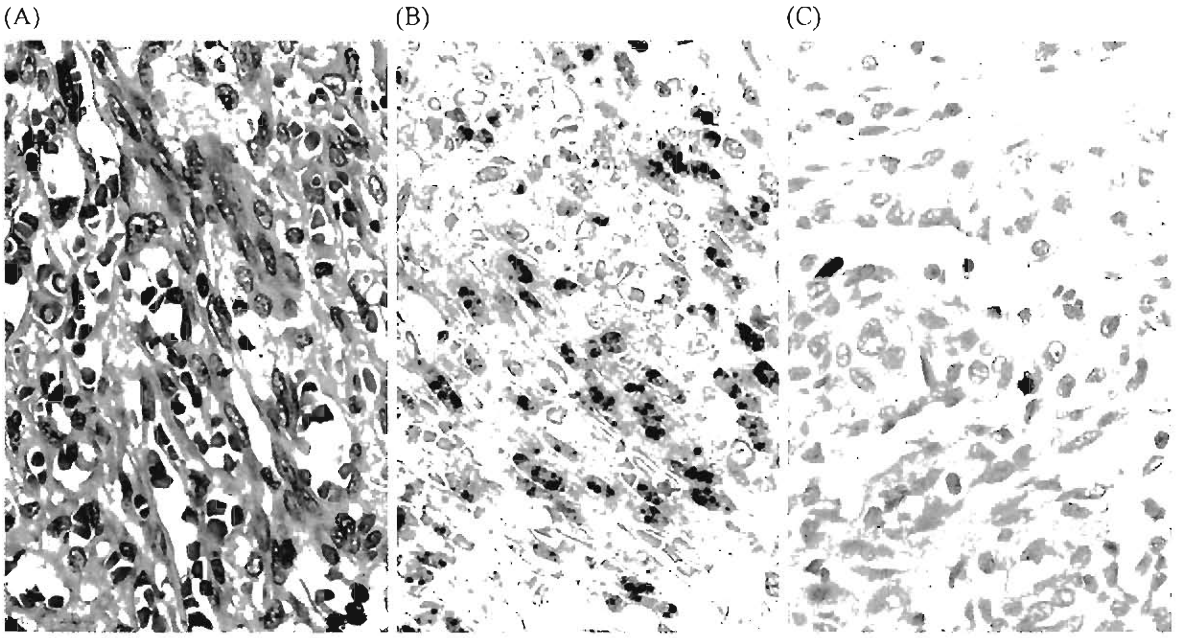

Fig. 3. Kaposi's sarcoma.
(A) HE staining. (B) Immunohistochemistry of ORF73, a latent protein. (C) Immunohistochemistry of ORF59, a lytic protein.

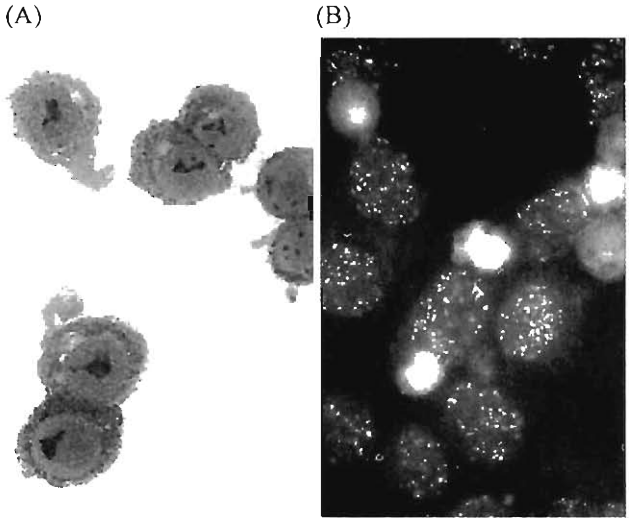

Fig. 4. Primary effusion lymphoma (PEL).
(A) Giemsa staining of an HHV-8-infected PEL cell line 'TY-1'.
(B) Immunofluorescence assay of HHV-8. Serum derived from a Kaposi's sarcoma patient was used as the primary antibody. Dot-like signals of LANA were found in the nuclei of TY-1 cells.

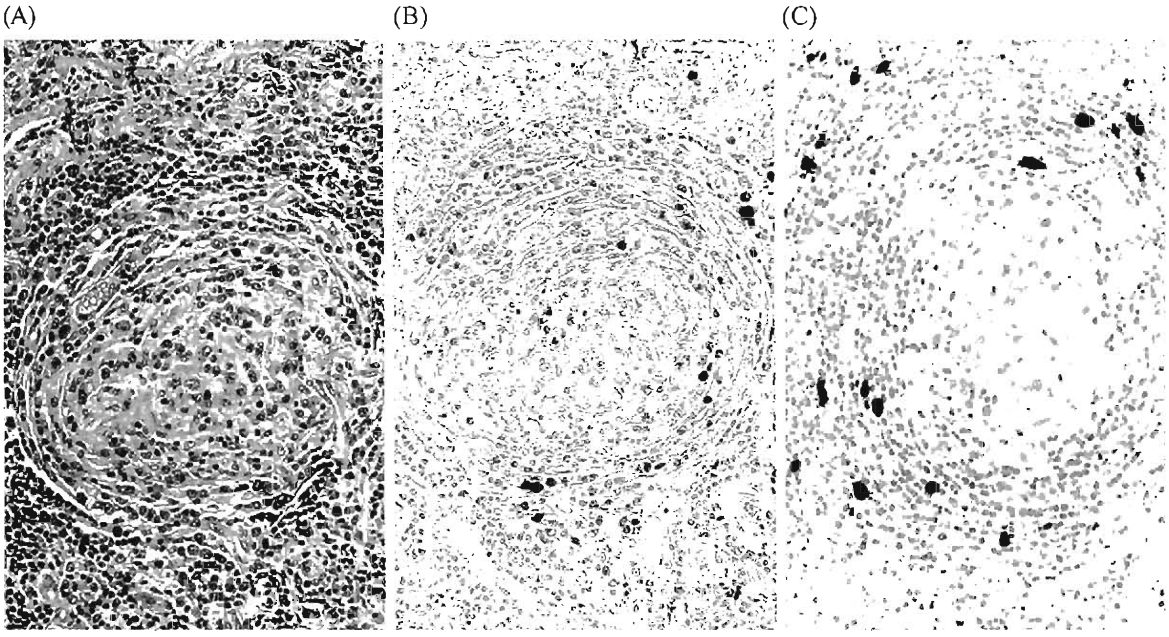

Fig. 5. Multicentric Castleman's disease (MCD).
(A) HE staining. (B) Immunohistochemistry of ORF73. (C) Immunohistochemistry of K8, a lytic protein.

sensitivity, were developed (69).

4. Epidemiology

4.1 Seroprevalence and transmission

Current HHV-8 antibody testing has some problems in terms of accuracy, as previously described, particularly in patients with asymptomatic HHV-8 infection (65). However, several groups have reported the seroprevalence of HHV-8 in the general population of various countries (Table 2). Positivity in these studies has varied from 0 to 53%, depending on the assay used and the countries where research was conducted (60, 63, 69, 72-74). Infection with HHV-8 seems to be uncommon in the United States (U.S.) (0 - 25%), Japan (1.4%) and Northern Europe (3 - 5.1%), common in certain Mediterranean countries (4 - 12%), and prevalent in African countries such as Uganda (35 - 53%) (Table 2). Generally, sera derived from KS patients are positive for HHV-8 antibodies regardless of HIV infection. The homosexual population exhibits a higher level of positivity than the heterosexual one.

The transmission modes of HHV-8 have not yet been clarified. In countries with an endemic infection, horizontal transmission among children is thought to be prevalent (63), while sexual transmission appears to play an important role among homosexual men in non-endemic countries (75). Recently, a large cohort study of Amsterdam homosexuals revealed that seroconversion of the antibodies against HHV-8 is associated with orogenital contact, and this study also indicated that the titer of the antibody against ORF65 increases in HIV-seronegative homosexuals but that against ORF73 increases earlier than that against ORF65 in HIV-infected ones (71). The study also revealed that orogenital sexual behavior

Table 2. Seroprevalence of HHV-8

Method	Antigen	Prevalence				
		HIV+/KS+	HIV+/KS−	HIV−/KS+	Population	Blood donor
IFA	PEL cell (LANA) (67, 206, 207)	67-88 %	12-56% Hemophilia; 0-3 %(67) STD; 28%(206) Homosexual; 30%(207)	51-94 %	0-12 % 1 % (women)(62) 53% (Uganda)(67)	0-5 % (USA) 0.2 % (Japan)(72) 4 % (Italy) (207) 3% (UK)(67)
	(lytic phase)(208)	83-96 %	61-69 %	100 %		20-28 %
WB	PEL (LANA) (84)	80 %	18 %			0 %
	ORF65 (166)	89 %	20 %			11 %
ELISA	ORF26 (peptide) (61)	60 %	27 %			20 %
	ORF65 (66)	92 %	24 %			5 %
	Whole virus lysate (60)	92 %	26 %	93 %		11 %
Combination IFA, ELISA	PEL, ORF65(67)	81.5 %	30-31 %	94 %	33-52%(Uganda)(63)	0-5 %(USA, UK) 43% (Uganda)(63)
IFA, ELISA, WB	PEL, ORF65(64)		30% (homosexual)		21% (homosexual)	
Mixed ELISA, & IFA, WB	ORF65, K8.1, ORF59, ORF73(LANA) PEL(69)	96%	63.6%(sexual) 0%(hemophilia)	100%	1.4%(Japan)	

was usually 'unprotected' unlike the anogenital sexual intercourse among Amsterdam homosexuals examined in the report. Taking into consideration the high copy number of the virus in saliva compared with that in semen (76), it is clear that saliva-mediated transmission is possible.

4.2 Molecular epidemiology

HHV-8 genomes are classified into several subgroups based on the sequence variability of the K1 gene (77,78). There are two hypervariable regions in the K1 gene. The two regions encode the extracellular domain of the K1 protein, and these variations are classified into at least four groups, i.e., A, B, C and D. Subtype A was mainly detected in AIDS-KS patients in the U.S., and subtype C was predominantly found in patients with the classic KS, iatrogenic and AIDS-KS in the Middle East and Asia. Subtype B was found in KS patients of African descent. Subtype D was rare and found in KS patients of Pacific Island descent. The geographical differences in HHV-8 infection may reflect the history of migration of human populations from Africa over the past 35,000 to 60,000 years (77).

5. HHV-8 related diseases

5.1 Kaposi's sarcoma (KS)

KS was first described in 1872 as a rare tumor occurring in elderly men of Mediterranean descent (classic type) (79). Recently, three additional clinical types, which are histologically indistinguishable, have been recognized: AIDS-associated, post-transplantational (iatrogenic or immunodeficient) and African (endemic) types (80). Skin lesions of KS are clinically classified into patchy, plaque and nodular stages. In the patchy stage, small red flat lesions are noted on the skin. These lesions fuse together to form plaque lesions (plaque stage) and later become brown nodular and elevated lesions in the nodular stage. These skin lesions appear mainly on the extremities but in more advanced cases appear as multiple ovoid-shaped skin lesions distributed symmetrically over the trunk. Organ involvements are sometimes observed in gastrointestinal tracts and/or the lungs, resulting in death. Histologically, the proliferation of spindle cells with slit-like vascular spaces is characteristically observed (Fig. 3A).

KS had been suspected to be an infectious disease because of the following reasons. 1) AIDS-KS occurs particularly in homosexual males. 2) The progression of KS depends on the host's immune status, and spontaneous regression of KS is sometimes reported. 3) The geographic distribution of KS in the world is restricted to certain regions. Prior to the identification of HHV-8, whenever any viruses were detected in KS patients, they were assumed to be infectious agents of KS. Therefore, the discovery of HHV-8 completed the search for etiological and infectious agents of KS. DNA fragments of HHV-8 can be detected in 95% of KS tissues by PCR regardless of their clinical subtypes (81,82). However, the copy number of this virus in spindle cells in KS tissues is low (approximately 1 copy per cell) (83). It has been demonstrated by various methods that almost all spindle cells in KS tissues are in the latent phase (41,42,57) (Fig. 3 B). The expression of lytic proteins is limited in KS lesions (Fig. 3C). Therefore, it is likely that latent infection with HHV-8 is important for the pathogenesis of KS.

Some types of cytokines have been detected in the sera of KS patients at high levels, and several of them, including beta fibroblast growth factor (bFGF), IL-6, onocostatin M (OSM) and tumor necrosis factor (TNF)-alpha, were shown to be required for the growth of KS cells in vitro. Among them, IL-6 is known to be an important growth factor of KS cells. HHV-8-encoded vIL-6 is detected in tissues of KS lesions. A recent report revealed that vIL-6 could stimulate the signaling pathway of human IL-6 (29); therefore, HHV-8 is probably associated with the formation of the cytokine network in KS lesions.

Serological evidence also supports the association of HHV-8 with KS pathogenesis. Anti-HHV-8 antibodies were detected in almost all sera derived from KS patients (69). In addition, homosexual males with AIDS, who belong to a group at high risk for KS, exhibit high seroprevalence of the antibody against HHV-8. Seroconversion of the antibodies against HHV-8 was observed before the appearance of KS lesions in both AIDS and organ-transplanted patients (70,71,84,85). These data indicate the specific relationship between KS and HHV-8 infection.

The mechanism of KS regression has been investigated. HHV-8-specific cytotoxic T lymphocytes (CTLs) against HHV-8-K12, K8.1 and K1 proteins were identified (86). We reported one case of KS regression, in which the depletion of HHV-8-infected cells was observed in the process of spontaneous regression (87). In this case, many CD8-positive CTLs infiltrated the KS lesions (87). These findings suggest that CTL response plays a central role in the regression of KS.

5.2 Primary effusion lymphoma (PEL)

PEL is a new disease entity described by Nador et al (88). This type of lymphoma appears as lymphomatous effusions occurring in the absence of a contiguous tumor mass. These effusions exhibit a distinctive morphology bridging large-cell immunoblastic lymphomas or anaplastic large-cell lymphomas (ALCLs) (Fig. 4A). Genetically, HHV-8-associated lymphoma cells lack *c-myc* gene rearrangements and *bcl-2*, *ras* and p53 gene alterations (88). A recent study revealed that frequent mutations in the *bcl-6* gene were detected in PEL cells, suggesting that PEL cells originate from the germinal center or the post-germinal center B cells (89). Their immunophenotypes are undetermined, i.e., CD45 (+), CD138 (+), B cell markers (–), and T cell markers (–); however, an immunoglobuline gene rearrangement was detected (88, 90). These lymphomas occur in HIV-infected homosexual males, which is the same as KS occurrence.

In 1995, HHV-8 was first detected in AIDS-associated BCBL (PEL) (83). PEL cells contain a high copy number (40-100 copies/cells) of HHV-8 DNA (83). PEL cells are sometimes coinfected with EBV, while others are infected only with HHV-8. However, expressions of LMPs and EBNAs are suppressed in PEL cells. Several HHV-8-infected cell lines have been established from PEL cells (2,5,91-95). We established an HHV-8-positive and EBV-negative cell line, TY-1, even from EBV-positive and HHV-8-positive PEL cases (91). These data suggest that HHV-8 plays an essential role in the pathogenesis of PEL.

Studies of the HHV-8-positive PEL cell lines have provided insights into the features of this virus. It has been demonstrated that all of the PEL cells express LANA, (Fig. 4B), suggesting that they are in the latent phase. It has also been shown that chemical stimulation using TPA converts the PEL cell lines from the latent phase to the lytic phase (2). Electronmicroscopy has revealed that many HHV-8 particles are found in the nuclei of TPA-treated cells (5) (Fig. 1). The fact that PEL cells produce IL-10, IL-6 and the receptors for

IL-6 suggests the presence of an autocrine loop for growth, which is the same as that of KS (96). Among HHV-8-encoded proteins, K9 (vIRF) is known to inhibit the interferon signaling pathway, and this suggests that K9 functions as an oncogene in PEL cells (49). However, the expression of K9 protein is restricted in PEL cells. Thus, further studies are required to clarify the oncogenic role of HHV-8 in the pathogenesis of PEL.

5.3 Multicentric Castleman's disease (MCD)

MCD is a rare disease characterized by plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia and high levels of IL-6 in the serum (97-99). Follicular hyperplasia with proliferation of plasma cells and hyaline vascular alterations in the lymph node are the histopathological hallmarks of MCD (Fig. 5A). In 1996, HHV-8 was first detected in some cases of MCD (100). Unlike in cases of KS and PEL, the HHV-8 genome is detected in only a small population of MCDs. However, HHV-8 DNA is frequently detected in tissues obtained from patients with MCD associated with HIV infection (100-102). Recently, HHV-8 was also detected with a high frequency in MCD complicated with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome (103).

Immunohistochemical studies revealed that HHV-8 infected cells are localized in the mantle zone of deformed lymphoid follicles and that the lytic and latent proteins encoded by HHV-8 are expressed in these cells (58, 104) (Fig. 5B and 5C). Lytic proteins including vIL-6 are also strongly expressed in MCD (58,102,104) (Fig. 5C). These data suggest that the role of HHV-8 in MCD differs from that in KS or PEL. Whether or not HHV-8-encoded vIL-6 plays a role in the proliferation of plasma cells is an important issue in elucidating the pathogenesis of HHV-8-associated MCD, since the level of IL-6 is high in the sera of patients with MCD.

Recently, Dupin et al. reported that HHV-8 was detected in plasmablasts of the plasmablastic variant of MCD (105). They also demonstrated that plasmablasts have a clonal lambda light chain and proposed that the plasmablastic lymphoma associated with MCD is a new disease entity which is also associated with HHV-8 infection.

5.4 AIDS-associated anaplastic large cell lymphoma (ALCL)

The existence of AIDS-associated ALCL has been discussed by some authors (106-111). However, the diagnostic criteria for ALCL are ambiguous and confusing in these reports. There is a general consensus that ALCL exhibits the following histopathological features: 1) anaplastic large blastic cell morphology with occasional horse-shoe-shaped/multiple nuclei and one or two prominent nucleoli; 2) much larger cells than those found in ordinary large cell lymphomas, with a greater cytoplasmic volume; and 3) growth in a cohesive sheet-like pattern (112). ALCL is classified as a T/null cell type lymphoma according to the revised European-American classification of lymphoid neoplasms (REAL classification) (112). Meanwhile, reported 'AIDS-ALCL' contained both B and T cell lymphomas.

We reported three cases of AIDS lymphoma with an anaplastic large cell morphology. Notably, all three cases were infected with HHV-8 (113). The cases were complicated with KS, PEL and MCD. In addition, we demonstrated that subcutaneous inoculation of SCID mice with PEL cells produced HHV-8-positive and EBV-negative tumors in the inoculated sites, while the tumor cells exhibited morphological characteristics similar to those of ALCL. These findings suggest that HHV-8 may be associated with solid lymphomas and that they can have an anaplastic large cell morphology. The lymphomas should be distinguished from classical ALCLs that are defined by the REAL classification even though their morphology and part of their immunophenotype mimic the classical ALCLs.

5.5 Others

DNA fragments of HHV-8 have been detected in certain diseases; however, the associations of HHV-8 with these diseases need to be elucidated. Rettig et al. reported that HHV-8 DNA was detected in bone marrow dendritic cells from multiple myeloma patients (114). However, there were both positive and negative reports using PCR (115-119) and serological techniques (120,121). Considering these papers, a definitive association of HHV-8 with myeloma cannot be made. HHV-8 DNA was also detected in lesions of sarcoidosis (122), Bowen's disease and various skin lesions of transplant patients (123); however, all these results are considered to be either false positives or not associated with the pathogenesis of the diseases.

6. Conclusion

Since the discovery of HHV-8, virological and molecular characteristics of HHV-8 have been studied extensively and actively. It was surprising that an almost complete sequence of the virus DNA was determined within only two years after its discovery. Currently, epidemiological and histopathological studies are ongoing, carried out by many researchers in various countries, which will elucidate the pathogenesis of HHV-8-associated diseases. Thus, HHV-8 has become one of the extensively studied viruses in the world. However, its oncogenesity and its association with the pathogenesis of KS, which are the focus of HHV-8 studies, have not been clarified as well as for other oncoviruses such as EBV, HPV, and human T-cell leukemia virus-I (HTLV-1). In this review, we suggest that latency is significant for the pathogenesis of HHV-8-associated malignancies. Virologically, the most significant issue in HHV-8 research is that permissive cells that replicate very efficiently have not yet been found. Therefore, it is difficult to perform infection experiments or to produce mutant viruses. The function of each viral protein will be investigated using transgenic mice or transfection studies; however, mutant viruses will be needed to investigate the role of each protein in the virus.

Another important aspect of HHV-8 studies in the future concerns virus transmission. Recently, mass cohort studies have been reported; however, major transmission modes remain unclear, particularly in countries where the virus is endemic. Studies on the natural history of HHV-8 infection will be essential to the HHV-8 research.

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