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Kaposi Sarcoma-Associated Herpesvirus (KSHV) or Human Herpesvirus 8 (HHV-8)

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Definition

Kaposi sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8) is a virus that is associated with the original AIDS-defining tumor, Kaposi sarcoma (KS). This virus is necessary for the development of KS. Expression of the viral protein, LANA, represents the definitive diagnostic marker for KS. In addition to KS, KSHV is also associated with primary effusion lymphoma and a plasmablastic variant of multicentric Castleman disease.

KSHV is a double-stranded DNA virus. There exists no vaccine against this virus. Viral DNA replication is sensitive to ganciclovir. The virus establishes lifelong latency in the infected host.

Introduction

The development of Kaposi sarcoma (KS) is linked to infection with Kaposi sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8). This association was established when Drs. Yuan Chang and Patrick Moore discovered viral DNA in KS biopsies, but not in the skin from healthy controls. KSHV is present in essentially every tumor cell within a KS lesion (Chang et al. 1994). Within each tumor cell, the viral latent proteins, as well as the viral microRNAs, are expressed. Other viral proteins may be expressed as well depending on tumor subtype and the particular signals that emanate from the tumor microenvironment, e.g., hypoxia can activate lytic replication and gene expression of specific KSHV genes (Davis et al. 2001). In addition to KS, KSHV also drives the pathology of primary effusion lymphoma (PEL) (Cesarman et al. 1995) and a plasmablastic variant of multicentric Castleman disease (MCD) (Carbone et al. 2009; Soulier et al. 1995). In KS and PEL the virus predominantly exists in its latent form and does not replicate to high levels. MCD may be an exception, since it is associated with high-level expression of the viral IL6 homologue and other lytic proteins. Primary infection or reactivation from tumor cells and latently infected $CD20^{+}$ B cells leads to systemic viremia, salivary shedding, and person-to-person transmission. In extremely severe cases, high-level viremia can lead to KS-associated inflammatory cytokine syndrome (KICS) (Polizzotto et al. 2012).

Transmission

KSHV is transmitted orally or by sexual routes, blood transfusion, or the transplantation of infected organs (reviewed in Bagni and Whitby (2009)). In endemic areas such as sub-Saharan Africa and the Mediterranean region, the prevalence of KSHV is high. KSHV is detected in breast milk and

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maternal saliva suggesting an oral route of transmission in children. Close family relatives are positive for viral DNA in their saliva, also suggesting an oral transmission route. By comparison to endemic and epidemic regions, Western Europe and the USA have a low prevalence of KSHV. Here the virus is thought to be transmitted sexually, particularly in men who have sex with men (MSM). The mechanism of transmission here may be largely through the use of saliva as a lubricant. The reason for this apparent geographic difference in transmission pattern is unknown. Blood-borne transmission, as well as transmission by a transplanted organ, can also occur. At present the blood supply even in endemic areas or for high-risk donors is not routinely screened for KSHV. It is noteworthy that unlike HIV, KSHV appears to be an old virus that coevolved with humans.

Kaposi Sarcoma

The incidence of KS reflects the prevalence of KSHV. In certain high-prevalence regions, such as sub-Saharan Africa, KS is not uncommonly seen in children, the elderly, and transplant recipients independent of HIV infection. Whether there exists a genetic susceptibility locus for KSHV infection or for the development of KS is currently unknown. KS is one of the most common cancers in sub-Saharan Africa where it causes significant morbidity and mortality (Jemal et al. 2012). HIV coinfection substantially increases the risk for developing KS. In Western Europe and the USA, the number of KS cases has declined since the introduction of combination antiretroviral treatment (cART), but KS still occurs even in the presence of high CD4 counts and low-HIV viral load (Krown et al. 2008). For example, KS rates in the San Francisco area for white men were ~30 per 100,000 during 1987–1991 (pre-cART era) and declined to 2.8 in 1998 (post-cART era). A further decline however did not happen and KS incidence in the US has stabilized since 2000. There are multiple epidemiological forms of KS:

(i) "Classic" KS afflicts elderly men of Mediterranean or eastern European origin. Classic KS occurs in the absence of HIV coinfection.
(ii) "Endemic" KS occurs in Central and Eastern Africa in the absence of HIV coinfection. It is often a disease of children or young adults.
(iii) "Transplant-associated" or iatrogenic KS develops in immunosuppressed individuals e.g., organ transplant patients. This also occurs in the absence of HIV coinfection.
(iv) "Epidemic" KS also known as AIDS-KS is the most common AIDS-defining cancer, which predominantly afflicts HIV-infected MSM, although women can also develop KS.

These forms intermix, as HIV is now prevalent in KS endemic areas, even in children, and HIV+ patients undergo organ transplantation. In addition KS has been noted to flare up shortly after the start of cART, a phenomenon that is called KS immune reconstitution inflammatory syndrome (KS-IRIS). KS is also seen in some cases of KSHV-associated herpesvirus inflammatory syndrome (KICS), which is a recently described clinical entity that is associated with high-level KSHV replication (Polizzotto et al. 2012).

Systemic KSHV viral load is associated with KS development and often precedes it. It is important to consider, however, that KSHV levels in the plasma of KS patients are low (200–30,000 copies) compared to other herpesviruses. There is no direct correlation between the severity of disease or number of lesions and KSHV viral load. This suggests that KS lesions result from the seeding of infected cells (analogous to traditional metastasis) as well as de novo infection of

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peripheral, lymphatic endothelial cells (reviewed in Ganem (2010)). In addition, local seeding and autocrine stimulation may help local KS lesions grow once they begin.

Kaposi Sarcoma-Associated Herpesvirus (KSHV): Genetic Structure

KSHV is a double-stranded DNA virus. Its genome is approximately 130,000 bp in length. A long unique region encodes all known viral proteins and is flanked on either end by a varying number of terminal repeat sequences. Upon circularization the terminal repeat sequences fuse and serve as the latent origin of replication and as the anchor point by which the viral extrachromosomal plasmid is tethered to the host chromosome. During latency the host cell DNA-dependent DNA polymerase is used to replicate the latent episomes. By contrast, lytic viral replication initiates at two conserved regions (oriLyt) and is dependent on the viral DNA-dependent DNA polymerase, as well as a complex of core replication proteins. The viral DNA polymerase is sensitive to ganciclovir, azidothymidine, foscarnet, and cidofovir, but not acyclovir. Two viral kinases (Orf36 and Orf21) mediate susceptibility to ganciclovir and azidothymidine.

KSHV encodes approximately 84 open reading frames. These can be categorized in multiple ways. Blocks of co-regulated proteins exhibit homology to other herpesviruses and mediate viral DNA replication, entry, capsid, envelope, and tegument formation. A second set of genes (K genes) are unique to KSHV or only present in the lymphotropic lineage of herpesviruses, which includes ► Epstein-Barr-Virus (EBV), as well as the monkey and mouse homologues of KSHV (reviewed in Chang and Moore (1996), and Damania (2004)). Several KSHV genes are homologues of human cellular genes and appear to have been acquired from the human genome.

KSHV Structure

KSHV virions exhibit an electron-dense capsid surrounded by a lipid bilayer envelope. In between the capsid and the envelope is a morphologically amorphous but highly organized proteinaceous layer called the tegument. The envelope is studded with viral glycoproteins, which engage host cell surface receptors and participate in viral entry. KSHV encodes seven glycoproteins: ORF22 (gH), ORF39 (gM), ORF47 (gL), ORF53 (gN), ORF68 (gB), and K8.1. Three of these, gB, gH, and gL, are required to mediate membrane fusion. The tegument contains multiple proteins and RNA transcripts. The herpesvirus tegument proteins are important as they are delivered into the target cell upon primary infection and may thus contribute to early reprogramming events before the synthesis of immediate-early proteins. The KSHV capsid architecture and polypeptide composition have been determined. Cryo-EM reconstruction has revealed that the icosahedral capsid is symmetric ($T = 16$) with 20 triangular faces. The building blocks are composed of hexamers and pentamers of the major capsid protein (MCP/ORF25) and interconnected by heterotrimer structures comprised of the minor capsid proteins ORF62 and ORF26 (Deng et al. 2008).

KSHV Entry

The virus enters target cells through multiple receptors and coreceptors (reviewed in Chandran (2010)). The $\alpha V\beta 3$ and $\alpha V\beta 5$ integrins serve as receptors for KSHV (Akula et al. 2001). The viral gB protein contains the signature integrin-binding RGD motif. Antibodies to either integrins or RGB

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peptides block entry. xCT is another receptor for KSHV. It is part of the cell surface CD98 (4F2 antigen) complex. Expression of xCT restores permissivity for KSHV and antibodies against xCT block infection. DC-SIGN (CD209) is also a receptor for KSHV. KSHV infection can be blocked by an anti-DC-SIGN monoclonal antibody and soluble DC-SIGN. Most recently, ephrin receptor A2 has been shown to act as a coreceptor of KSHV by binding to the viral gH and gL proteins (Hahn et al. 2012). Lastly, heparin sulfate increases the efficiency of infection. Since this virus enters multiple cell types (B lymphocytes, monocytes, endothelial cells, epithelial cells), different receptors may be utilized in different cell lineages; they may be essential for some cells but only serve auxiliary roles in others.

Upon entry, the virus immediately triggers an innate host response and induces interferon. In monocytes, KSHV activates TLR3 resulting in its upregulation and induction of downstream mediators, including IFN-β1 and the chemokine CXCL10 (also called IP-10). In plasmacytoid dendritic cells (pDCs), which are the chief IFN-producing cells in the body, KSHV activates TLR9 (reviewed in West et al. (2012)). In endothelial cells KSHV downregulates TLR4.

KSHV Gene Regulation

Many of the studies of KSHV gene regulation have been done in PEL cell lines. These studies have shown that viral reactivation, replication, egress, and infectious virion production can be triggered by a variety of signaling pathways (reviewed in Mesri et al. (2010)). The initial trigger event leads to the coordinated transcription of three kinetic classes of transcripts: those encoding immediate-early proteins (RTA/Orf50, K-bZIP), those encoding early proteins (MTA/Orf57, polymerase and its associated factors, vGPCR/Orf74), and those encoding late genes (capsid and tegument proteins).

The viral immediate-early transactivator RTA is necessary and sufficient to initiate KSHV viral replication (reviewed in Deng et al. (2007) and Staudt and Dittmer (2007)). The KSHV *Rta* gene encodes a 691-amino-acid protein that is highly phosphorylated and localizes to the nucleus of mammalian cells. Deletion of 160 amino acids in the C-terminal activation domain of the KSHV Rta/ORF50 results in the production of a truncated but stable Rta/ORF50 protein. This truncated Rta/ORF50 protein forms multimers with wild-type Rta/ORF50 in PEL cells and functions as a dominant negative inhibitor of Rta/ORF50. A KSHV deletion mutant missing the Rta gene is unable to reactivate upon chemical treatment. Rta/ORF50 is present in KSHV virions, i.e., it can be considered a virion transactivator and thus ensures lytic replication upon primary infection. Rta/ORF50-responsive promoters fall into one of two subgroups: those where Rta/ORF50 directly binds promoter DNA and those where Rta/OrRF50 does not directly bind promoter DNA, but rather transactivates the promoter by establishing protein-protein interactions with cellular transcription factors that mediate sequence-specific DNA binding. Most important among these interactions is the binding of Rta/ORF50 to cellular RBP-Jκ to modulate KSHV transcription. RBP-Jκ is a sequence-specific DNA-binding protein that is a downstream effector of cellular Notch signal transduction. KSHV can usurp the function of cellular RBP-Jκ without the requirement for Notch-ligand interaction, as the binding of KSHV Rta/ORF50 protein to RBP-Jκ converts RBP-Jκ from a transcriptional repressor to a transactivator.

Of note, the pattern of KSHV gene transcription is not as rigid as for other herpesviruses. Specific signaling stimuli and cellular environments can induce specific and sporadic transcription patterns. Stimuli that sporadically activate the transcription of oncogenic viral proteins, such as K1, viral interleukin-6 (vIL-6), or vGPCR, in the absence of complete replication (which would destroy the

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infected cell) are thought to contribute to oncogenesis in a paracrine fashion. Periodic reactivation and reinfection cycles are also thought to contribute to viral persistence in endothelial lineage cells.

Histone deacetylase inhibitors (vorinostat, valproic acid, sodium butyrate), signaling inducers such as TPA (Renne et al. 1996), and ligands for Toll-like receptors (TLRs) such as TLR7/8 agonists can induce KSHV reactivation from latency in culture. Interferon-alpha does not induce KSHV in its entirety, but only the expression of specific viral genes, e.g., the vIL-6 protein.

KSHV Carcinogenesis

All KS and PEL cells consistently express the viral latent proteins LANA/Orf73, vCyclin/Orf72, vFLIP/Orf71, kaposin, the viral microRNAs, and one or more of the viral interferon regulatory factor (vIRF) homologues (Dittmer 2011). These exhibit transforming activities in specialized assays. Other viral proteins like K1, vIL6, and vGPCR are strongly transforming in multiple assays in culture. They are expressed at low and varying levels in latent KSHV-infected cells but are highly upregulated during the lytic replication cycle. Abrogation either of latent proteins, latent protein-induced signaling, receptor-induced signaling, or purging of the viral episome is incompatible with tumor growth, demonstrating that KSHV is required for KS.

LANA is the major latency protein involved in latent viral replication and maintenance of the latent genome. LANA tethers the viral episome to histones on the host chromosome. During normal cell division, viral genomic DNA is replicated and segregated along with host chromosomes, thereby ensuring that each of the daughter cells also contain viral genomes. LANA also functions to augment cell proliferation and survival. LANA has been shown to bind the tumor suppressors p53 and Rb (reviewed in Ballestas and Kaye (2011) and Damania and Pipas (2009)).

LANA, vCyclin, and vFLIP are expressed on a polycistronic transcript. vFLIP is a viral homologue of cellular FLIP (FLICE [protein FADD-like interleukin-1 beta-converting enzyme, now called caspase-8] inhibitory protein). vFLIP strongly activates the NFκB signaling pathway and is thought to contribute to KSHV-associated oncogenesis (reviewed in Mesri et al. (2010)). Another latency-associated protein is vCyclin; vCyclin is a homologue of cellular cyclin D. vCyclin binds and activates CDK6 and is thought to promote S-phase entry. vCyclin transgenic mice develop lymphomas only in the context of p53 deficiency (reviewed in Damania and Pipas (2009)).

A working model of how the different molecular effectors that are encoded by KSHV work together to bring about the molecular phenotypes that are associated with KSHV infection can be constructed based on our knowledge of homologous viruses. The related gammaherpesvirus, herpesvirus saimiri (HVS), only requires two proteins, STP and TIP, to transform human T cells in culture, yet it encodes homologues of many of the genes of KSHV, which function primarily in modulating host interactions, in vivo persistence, and pathogenesis. The KSHV K1 protein can functionally substitute for STP and engages signaling pathways, principally PI3K/AKT/mTOR, through its ITAM motif. Whereas K1 is located on the left end of the KSHV genome, K15 another viral receptor signaling protein is located on the right side. K15 engages TRAFs 1, 2, and 3, which leads to the activation of NFκB and NFκB-regulated cytokines. It also triggers mitogen-activated protein kinase (MAPK) signaling. The KSHV K1 and K15 proteins appear to phenocopy the two principal EBV-transforming genes LMP1 and LMP2A (reviewed in Damania (2004)), thus establishing a receptor-initiated signaling environment as a common theme for all lymphotropic herpesviruses.

KS is arguably one of the most angiogenic tumors that arises in the human population. It is thought that KSHV viral proteins expressed in endothelial (and surrounding epithelial cells) induce

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the overexpression of angiogenic factors like vascular endothelial growth factor (VEGF). vGPCR, K1, and vIL-6 have been shown to induce VEGF and function to stimulate angiogenesis in a paracrine fashion (reviewed in Mesri et al. (2010)). KSHV infection can also reprogram endothelial cells creating a gene expression phenotype that is intermediate between blood and lymphatic endothelium (reviewed in Dimaio and Lagunoff (2012) and Hong et al. (2004)).

Please note that the clinical and systemic manifestations of KSHV infection and KSHV-associated cancers are discussed elsewhere (Ablashi et al. 2002; Dittmer and Krown 2010).

KSHV MicroRNAs

The most recent addition to our understanding of KSHV biology has been the discovery of the KSHV microRNAs (miRNA). KSHV encodes 12–20 mature miRNAs (reviewed in Cullen (2011) and Skalsky and Cullen (2010)). Each mature miRNA is made from a looped, double-stranded pre-miRNA. Depending on cell type and the exact RNA sequence, one or the other strands are preferentially processed and incorporated into the active RISC complex. Hence, there exists extensive variation in the count of mature miRNAs. KSHV miRNAs are expressed in KS and PEL and together with the cellular miRNA profile can be used to distinguish stages of KSHV infection. At present the function of all the miRNAs is not completely known. Thrombospondin 1, TGF-beta, and Bach1 are examples of some proteins known to be targeted by the KSHV miRNAs. Analogous to viral proteins, which mimic functions of host proteins, some viral miRNAs also share seed sequence (and therefore the same target range) as cellular miRNAs, most notably miR-K12-11 and miR-155. Downregulation of cellular miR-155 has been implicated in terminal plasma cell differentiation and it can be reasoned that by ectopically expressing an ortholog, KSHV can stall this process.

KSHV Immune System Interactions

Equally important to carcinogenesis is the means by which KSHV proteins modulate the immune system (reviewed in Lee et al. (2010) and Moore and Chang (2003)). These events may have systemic effects long before the development of clinically apparent lymphoma and KS. For instance, KSHV encodes a homologue to CD200/Ox2. Cellular CD200 is a negative regulator of inflammation. CD200 knockout mice exhibit increased susceptibility to experimentally induced autoimmune disease. The viral homologue of CD200, K14, is soluble and can bind to the CD200 receptor. How exactly this event modulates target cell function is not currently known.

KSHV also encodes homologues to cellular interferon regulatory factors (IRFs). The cellular IRFs transmit the activating signals from TLR or IFN alpha/beta receptors to the nucleus. This initiates and subsequently increases interferon production in a positive feedback loop. KSHV encodes four viral IRFs, vIRF1–4. The vIRF3 protein is constitutively expressed in latently infected PEL; vIRF1 is expressed in latent KS cells, whereas vIRF2 and vIRF4 have thus far only been seen upon lytic infection. vIRF1, 2, and 3 interfere with IFN signaling. The molecular mechanism by which these proteins function is quite varied. For example, vIRF1 binds to cellular IRF-1 and IRF-2 and inhibits these proteins in a classical dominant negative mechanism. However, vIRF1 also binds to CBP/p300, p53, and Bim. For a more detailed review of the function of the four vIRFs, please see review article Jacobs and Damania (2011).

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As mentioned above, KSHV encodes for a viral IL6 homologue, vIL-6 (reviewed in Sin and Dittmer (2012)). Unlike human IL-6, vIL-6 does not need to bind to the gp80 subunit of the IL-6 receptor complex to activate signal transduction. vIL-6 has been shown to activate cell signaling in an intracrine, autocrine, and paracrine fashion. vIL-6 can augment cell survival, prevent apoptosis, and activate angiogenesis through the upregulation of the proangiogenic factors, VEGF and angiopoietin 2. Depletion of vIL-6 in PEL has also been shown to inhibit their ability to proliferate.

In addition to coding for a viral IL6 homologue as described above, KSHV also encodes homologues to cellular inflammatory cytokines. These are vCCL1/vMIP-I/ORFK6), vCCL-2/vMIP-II/ORFK4), and vCCL-3/vMIP-III/ ORF K4.1). KSHV vCCL-1 signals through CCR8; vCCL-2 signals through CCR8 and CCR3; and vCCL-3 signals through CCR4. Thus, these KSHV chemokines activate chemokine receptors that are present on CD4+ Th2 cells. vCCL-2 can also bind to multiple other chemokine receptors, but this binding is nonproductive and therefore diminishes signaling through the cognate, cellular ligand.

Conclusion

KSHV encodes an arsenal of viral proteins that control cell proliferation, cell survival, and angiogenesis. Moreover, KSHV viral proteins help the virus evade both adaptive and innate immune responses in the infected host. Several KSHV proteins are homologues of cellular proteins, while others are uniquely encoded by KSHV. By modulating cellular signaling, apoptotic, and immune pathways in the infected cell, KSHV creates an environment that maintains virus survival and allows for virus dissemination and spread within the infected individual, as well as viral transmission from person to person. By commandeering the host environment in the aforementioned ways, KSHV infection may inadvertently result in cellular transformation and subsequent malignancy in some infected and susceptible hosts.

References

Ablashi DV, Chatlynne LG, Whitman Jr JE, Cesarman E. Spectrum of Kaposi's sarcoma-associated herpesvirus, or human herpesvirus 8, diseases. Clin Microbiol Rev. 2002;15:439–64.

Akula SM, Wang FZ, Vieira J, Chandran B. Human herpesvirus 8 interaction with target cells involves heparan sulfate. Virology. 2001;282:245–55.

Bagni R, Whitby D. Kaposi's sarcoma-associated herpesvirus transmission and primary infection. Curr Opin HIV AIDS. 2009;4:22–6.

Ballestas ME, Kaye KM. The latency-associated nuclear antigen, a multifunctional protein central to Kaposi's sarcoma-associated herpesvirus latency. Future Microbiol. 2011;6:1399–413.

Carbone A, Cesarman E, Spina M, Gloghini A, Schulz TF. HIV-associated lymphomas and gamma-herpesviruses. Blood. 2009;113:1213–24.

Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med. 1995;332:1186–91.

Chandran B. Early events in Kaposi's sarcoma-associated herpesvirus infection of target cells. J Virol. 2010;84:2188–99.

Chang Y, Moore PS. Kaposi's Sarcoma (KS)-associated herpesvirus and its role in KS. Infect Agents Dis. 1996;5:215–22.

DOI 10.1007/978-1-4614-9610-6_17-1

Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266:1865–9.

Cullen BR. Herpesvirus microRNAs: phenotypes and functions. Curr Opin Virol. 2011;1:211–5.

Damania B. Oncogenic gamma-herpesviruses: comparison of viral proteins involved in tumorigenesis. Nat Rev Microbiol. 2004;2:656–68.

Damania B, Pipas JM. DNA tumor viruses. New York: Springer; 2009.

Davis DA, Rinderknecht AS, Zoeteweij JP, Aoki Y, Read-Connole EL, Tosato G, Blauvelt A, Yarchoan R. Hypoxia induces lytic replication of Kaposi sarcoma-associated herpesvirus. Blood. 2001;97:3244–50.

Deng H, Liang Y, Sun R. Regulation of KSHV lytic gene expression. Curr Top Microbiol Immunol. 2007;312:157–83.

Deng BI, O'Connor CM, Kedes DH, Zhou ZH. Cryo-electron tomography of Kaposis sarcoma-associated herpesvirus capsids reveals dynamic scaffolding structures essential to capsid assembly and maturation. J Struct Biol. 2008;161(3):419–27.

Dimaio TA, Lagunoff M. KSHV induction of angiogenic and lymphangiogenic phenotypes. Front Microbiol. 2012;3:102.

Dittmer DP. Restricted Kaposi's sarcoma (KS) herpesvirus transcription in KS lesions from patients on successful antiretroviral therapy. MBio. 2011;2:e00138–00111.

Dittmer DP, Krown SE. Molecular basis for therapy of AIDS-defining cancers. New York: Springer; 2010.

Ganem D. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. J Clin Invest. 2010;120:939–49.

Hahn AS, Kaufmann JK, Wies E, Naschberger E, Panteleev-Ivlev J, Schmidt K, Holzer A, Schmidt M, Chen J, Konig S, Ensser A, Myoung J, Brockmeyer NH, Sturzl M, Fleckenstein B, Neipel F. The ephrin receptor tyrosine kinase A2 is a cellular receptor for Kaposi's sarcoma-associated herpesvirus. Nat Med. 2012;18:961–6.

Hong YK, Foreman K, Shin JW, Hirakawa S, Curry CL, Sage DR, Libermann T, Dezube BJ, Fingeroth JD, Detmar M. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet. 2004;36:683–5.

Jacobs S, Damania B. The viral interferon regulatory factors of KSHV: immunosuppressors or oncogenes? Front Microbiol Immunol. 2011;2:19

Jemal A, Bray F, Forman D, O'Brien M, Ferlay J, Center M, Parkin DM. Cancer burden in Africa and opportunities for prevention. Cancer. 2012;118:4372–84.

Krown SE, Lee JY, Dittmer DP. More on HIV-associated Kaposi's sarcoma. N Engl J Med. 2008;358:535–6; author reply 536.

Lee HR, Lee S, Chaudhary PM, Gill P, Jung JU. Immune evasion by Kaposi's sarcoma-associated herpesvirus. Future Microbiol. 2010;5:1349–65.

Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer. 2010;10:707–19.

Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus immunoevasion and tumorigenesis: two sides of the same coin? Annu Rev Microbiol. 2003;57:609–39.

Polizzotto MN, Uldrick TS, Hu D, Yarchoan R. Clinical manifestations of Kaposi sarcoma herpesvirus lytic activation: Multicentric Castleman disease (KSHV-MCD) and the KSHV inflammatory cytokine syndrome. Front Microbiol. 2012;3:73.

DOI 10.1007/978-1-4614-9610-6_17-1

Renne R, Zhong W, Herndier B, McGrath M, Abbey N, Kedes D, Ganem D. Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. Nat Med. 1996;2:342–6.

Sin SH, Dittmer DP. Cytokine homologs of human gammaherpesviruses. J Interferon Cytokine Res Off J Int Soc Interferon Cytokine Res. 2012;32:53–9.

Skalsky RL, Cullen BR. Viruses, microRNAs, and host interactions. Annu Rev Microbiol. 2010;64:123–41.

Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, d'Agay MF, Clauvel JP, Raphael M, Degos L, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood. 1995;86:1276–80.

Staudt MR, Dittmer DP. The Rta/Orf50 transactivator proteins of the gamma-herpesviridae. Curr Top Microbiol Immunol. 2007;312:71–100.

West JA, Gregory SM, Damania B. Toll-like receptor sensing of human herpesvirus infection. Front Cell Infect Microbiol. 2012;2:122.