Table 2 | Kaposi's sarcoma-associated herpesvirus genotypes.

Genotype	Patients, infected persons
A	AIDS–KS patients in the US, Europe, Eurasia
B	KS patients of African heritage
C	Classic KS, iatrogenic, and AIDS–KS in Eurasia, US AIDS–KS, Taiwan, Korea, China, Middle East
D	KS patients of Pacific island
E	South American (partial), Brazil Amerindian, Guinea Amerindian

50% in most of sub-Saharan Africa (Davis et al., 1997; Kedes et al., 1997; Chatlynne et al., 1998; Mayama et al., 1998; Rabkin et al., 1998; Katano et al., 2000a). The homosexual population exhibits higher positivity (8–25%) than the general population (Grulich et al., 2005; Casper et al., 2006; Engels et al., 2007). Although the transmission modes of KSHV have not yet been clarified, transmission though saliva is likely (Pauk et al., 2000), because high KSHV copy numbers are detected in saliva of seropositives. Horizontal transmission through the saliva transmission is suggested among children in endemic countries, while sexual transmission may be predominant among homosexual men in non-endemic countries. Organ transplantation can transmit KSHV (Regamey et al., 1998). Transmission of KSHV through blood transfusion is controversial. While KSHV seroconversion was found in US transfusion recipients (Hladik et al., 2006), later studies found no significant association of KSHV infection between transfusion groups and non-transfusion groups (Cannon et al., 2009).

Genotypes of KSHV are categorized based on sequences of the hypervariable regions in its *K1* gene (Meng et al., 1999; Zong et al., 1999; Biggar et al., 2000; Kazanji et al., 2005; Hayward and Zong, 2007; Kanno et al., 2010). The KSHV *K1* genes are classified into at five groups: A, B, C, D, and E (**Table 2**). Geographical differences in KSHV genotypes may reflect the history of migration of human populations (Zong et al., 1999). Subtypes A and C were detected in Japan and subtype A was seen more frequently in AIDS-associated cases than non-AIDS patients (Kanno et al., 2010). There is no correlation between genotype and KSHV-related disease, including KS, PEL, and multicentric Castleman's disease (MCD).

KSHV-RELATED DISEASES

Fragments of the KSHV genome have been detected in DNA samples extracted from various diseases by PCR. However, the only diseases whose associations with KSHV infection are widely accepted among researchers in this field are KS, PEL, and MCD (**Table 3**). KSHV is distributed all over the world, and there are many individuals with KSHV infections. Therefore, a low KSHV titer, as detected by PCR, does not mean that a disease is associated with KSHV infection. Because KSHV LANA-1 is always expressed in KSHV-infected cells, LANA-1 immunohistochemistry is a powerful and confirmative tool to detect KSHV-infected cells in pathological samples, and the association with KSHV infection in diseases should be examined by LANA-1 immunohistochemistry on tissue samples.

Table 3 | Kaposi's sarcoma-associated herpesvirus and diseases.

Usually detected (Confirmed association in all cases)	Kaposi's sarcoma (all subtypes), primary effusion lymphoma
Partially detected (Confirmed association only in KSHV$^+$ cases)	Multicentric Castleman's disease including POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome, febrile maculopapular skin rash, hemophagocytic syndrome
Detected in reports, but no association with KSHV infection	Multiple myeloma, primary pulmonary hypertension, Bowen disease, squamous cell carcinoma, Paget disease, actinic keratosis etc.

PRIMARY KSHV INFECTION

A mass study of immunocompetent children in Egypt, where KSHV infection is common, suggested that a febrile maculopapular skin rash was associated with primary KSHV infection (Andreoni et al., 2002). Seroconversion for KSHV was confirmed in those patients and transmission through saliva was implied by DNA sequences in saliva. A study of homosexual men without HIV infection suggested that diarrhea, fatigue, localized skin rash, and lymphadenopathy were also symptoms of primary KSHV infection (Wang et al., 2001). Moreover, active KSHV infection may be associated with non-malignant illnesses such as fever, cutaneous rash, and hepatitis after peripheral blood stem cell/bone marrow transplantation (Luppi et al., 2000).

KAPOSI'S SARCOMA

Kaposi's sarcoma is most important and common of KSHV-associated diseases. Four clinical subtypes have been recognized: classic, AIDS-associated, post-transplantational (iatrogenic or immunodeficient), and African (endemic) subtypes (Antman and Chang, 2000). These four subtypes of KS are histologically indistinguishable. In the AIDS–KS subtype, KS occurs only in homosexual men. KS occurs in the skin, oral cavity, gastrointestinal tract, lung, liver, lymph node, etc. Skin lesions of KS are most common; they are clinically classified as patchy, plaque, and nodular stages. In the patchy stage, small red flat lesions are observed on the skin. Histologically, dilated, abnormally shaped blood vessels with extravasated red blood cells and edema are found in KS lesions. In the plaque stage, patchy lesions fuse together to form plaque lesions. Proliferation of the spindle-shaped cells is seen around vessels in the plaque stage. In the final nodular stage, brown nodular, and elevated lesions are observed. Histologically, proliferation of spindle cells with slit-like vascular spaces is found (**Figure 1A**). Multiple KS lesions in the extremities or face are often complicated with lymphedema. Pulmonary lesions may lead to fatal respiratory compromise.

Kaposi's sarcoma should be diagnosed with histology and immunohistochemistry. Immunohistochemical staining with anti-LANA-1 antibody shows that the viral protein is expressed in KS cells, irrespective of clinical type or disease stage (Dupin et al., 1999; Katano et al., 1999b). Expression of LANA-1 can be seen in nuclei of KS spindle cells with a speckled pattern (**Figure 1B**). The

lymphatic marker, podoplanin (D2-40), is also expressed in KS cells (Weninger et al., 1999). In addition to histological investigation, PCR analysis is useful for the KS diagnosis. Because each KS cell contains about one copy of the KSHV genome, KSHV DNA fragments are consistently detected by PCR, even in formalin-fixed paraffin-embedded KS tissues (Asahi-Ozaki et al., 2006). PCR sometimes, but not always, detects KSHV DNA in the sera of KS patients. Serum antibody to KSHV is usually positive in KS patients.

Highly active anti-retroviral therapy (HAART) is effective on KS. Incidence of KS in HIV-infected persons has dramatically decreased in the HAART era. Regression of KS is often observed in patients administrated with HAART. In patients with low CD4 counts, KS progresses earlier than in patients with high CD4 counts. These data suggest that KS progression depends on the host's immune status (Bower et al., 2009). Recently, patients with KS were administrated with HAART. Patients with aggressive KS received a combination therapy of HAART and chemotherapy of pegylated liposomal doxorubicin (Martin-Carbonero et al., 2008). Irradiation or surgical resection is also performed for the case of small skin lesion in addition to HAART. There is no effective anti-KSHV therapy for KS. Although vaccine is the most effective method to prevent viral diseases, no vaccine against KSHV is commercially available at present.

The pathological roles of KSHV in KS have been intensely investigated for a long time. The origin of KS cells is thought to be endothelial cells. However, cellular protein expression in KS cells is very different from those of endothelial cells. Infection by KSHV induces a dynamic alteration of gene expression in endothelial cells (Hong et al., 2004; Wang et al., 2004). Analysis via DNA array revealed that endothelial cells reduce expression of blood vascular genes and induce markers of lymphatic endothelial cells after KSHV infection *in vitro*. Thus, KSHV can affect the expression level of cellular proteins in endothelial cells. LANA-1 is expressed in the nucleus by almost all KS spindle shaped cells (**Figure 1B**), whereas the expression of lytic proteins is limited in KS lesions. Therefore, it is likely that latent infection by KSHV is important for the pathogenesis of KS. As described above, LANA-1 plays a central role in the establishment and maintenance of latency. In addition to LANA-1, cytokines are important for KS pathogenesis. Some cytokines have been detected in the sera of KS patients at high levels. It has been demonstrated that bFGF, IL-6, oncostatin M (OSM), and tumor necrosis factor (TNF)-alpha are required for growth of KS cells *in vitro* (Liu et al., 1997; Faris et al., 1998; Murakami-Mori et al., 1998). IL-6 is known to be an important growth factor of KS cells especially *in vitro*. KSHV-encoded vIL-6 interacts with the receptor of human IL-6, mimics its function partially, and contributes to immune escape mechanism by KS cells as described above. KSHV-infected cells have several immune escape mechanisms besides that of vIL-6. K5, a lytic protein of KSHV, down-regulates MHC class I and co-activation molecules, enabling productively infected cells to escape both cytotoxic T cell and NK cell responses (Ishido et al., 2000). In addition, latently infected cells are also resistant to cytotoxic T cell responses owing to reduced levels of MHC class I molecules, impaired antigen processing, and expression of the anti-apoptotic KSHV ORF-K13/viral FLICE-inhibitory protein (v-FLIP; Thome et al., 1997).

PRIMARY EFFUSION LYMPHOMA

Primary effusion lymphoma is a rare disease occurring mainly in immunosuppressed patients, in particular HIV-infected homosexual males (Cesarman et al., 1995; Nador et al., 1996). PEL appears as lymphomatous effusions occurring in the pleural, abdominal, or pericardial effusion in the absence of a contiguous tumor mass. Some patients with PEL secondarily develop solid tumors in adjacent structures such as the pleura; these solid tumors have been termed extracavity PEL (Chadburn et al., 2004). About half of PEL patients have KS. These tumors always carry KSHV and are commonly co-infected by EBV. Histologically, the tumor cells exhibit various appearances, from large immunoblastic or plasmablastic cells to cells with more anaplastic morphology (**Figure 1C**). Nuclei vary from large and round to more irregular in shape, with prominent nucleoli. The cytoplasm can be abundant and is deeply basophilic with vacuoles in occasional cells. Binucleated or multinucleated cells resembling Reed–Sternberg cells can be seen. Mitotic figures are typically numerous. PEL cells are derived from post-germinal center B-cells (Jenner et al., 2003). Their immunophenotypes are undetermined, i.e., CD45 (+), CD138 (+), B-cell markers (−), T cell markers (−); however, their immunoglobulin genes are clonally rearranged and hypermutated. PEL cells contain high copy numbers (about 50 copies/cells) of KSHV DNA (Cesarman et al., 1995; Asahi-Ozaki et al., 2006). PEL cells are sometimes co-infected with EBV, while others are infected only with KSHV. However, expressions of LMPs and EBNAs are suppressed in PEL cells. Several KSHV-infected cell lines have been established from PEL cells (Carbone et al., 2010). A $KSHV^+/EBV^-$ cell line, TY-1, was even established from EBV^+ and $KSHV^+$ PEL cases, suggesting that KSHV plays an essential role in the pathogenesis of PEL (Katano et al., 1999a). Infection by KSHV is predominantly latent in PEL cells, which has made PEL cell lines the most widely studied models for KSHV latency. PEL cells express latent genes coded in the latent cluster in KSHV genome (**Figure 1D**). However, it is not easy to detect latent viral protein expressions other than LANA-1. The expression pattern of KSHV-encoded proteins is almost the same as KS, except that PEL cell express LANA-2 protein (Rivas et al., 2001). Most PEL lines display a very small subpopulation of cells that stain for markers of lytic reactivation such as ORF50, ORF59, and K8.1 (Katano et al., 2000b). Although KSHV-encoded vIL-6 is thought as a lytic protein, vIL-6 is detected more frequently in PEL cells than other lytic proteins. It has been demonstrated that vIL-6 is a multifunctional protein; vIL-6 can bind to IL-6 receptor gp130 in the absence of another subunit of IL-6 receptor, gp80, suggesting vIL-6 can induce cytokine signals in a broader range of cell types (Chatterjee et al., 2002). The signal from gp130 often secretes human IL-6 itself, raising the possibility of an autocrine loop. vIL-6 also induces VEGF expression, resulting in an indirect proliferation effect on PEL cells (Aoki et al., 1999).

MULTICENTRIC CASTLEMAN'S DISEASE

Multicentric Castleman's disease is characterized by plasmacytic lymphoadenopathy with polyclonal hyperimmunoglobulinemia

and high levels of IL-6 in the serum. Histologically, follicular hyperplasia with proliferation of plasma cells and hyaline vascular alterations are observed in the lymph nodes (**Figure 1F**). Two distinct histopathologic subtypes have been reported; the hyaline vascular type (HV type) and the plasma cell type (PC-type). The HV type is characterized by enlarged lymphoid follicles, hyalinized germinal centers within an expanded mantle zone, and a highly vascularized interfollicular area. In contrast, in the PC-type, remarkable infiltration of plasma cells is observed in the interfollicular area. Among these mantle zone cells, there are variable numbers of the larger cells, which are approximately twice the size of mantle zone lymphocytes. These cells are characterized by a moderate amount of amphophilic cytoplasm and a large vesicular nucleus containing one or sometimes two prominent nucleoli. These cells have been called plasmablasts, although they frequently have immunoblastic features (Dupin et al., 2000). The plasmablasts are also found in the interfollicular area of PC-type MCD frequently. In some, but not all cases of MCD, KSHV is detected (Soulier et al., 1995). Using PCR, KSHV is frequently detected in tissues obtained from patients with MCD associated with HIV infection, but is very rare in MCD cases without HIV infection (Suda et al., 2001). KSHV was also detected with high frequency in MCD complicated with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome (Belec et al., 1999). Immunohistochemistry for LANA-1 revealed that KSHV-infected cells are localized in the mantle zone of lymphoid follicles (**Figure 1G**). Besides LANA-1, other KSHV-encoded lytic proteins such as vIL-6, K8, and K8.1 are also detected in these cells, suggesting KSHV$^+$ MCD is associated with KSHV-lytic infection (Dupin et al., 1999; Katano et al., 2000b). The KSHV-encoded vIL-6 plays a role in the proliferation of plasma cells, and is also detected in patients' sera at high levels, suggesting high levels of vIL-6 are associated with MCD pathogenesis (Parravicini et al., 1997). High levels of KSHV DNA are also detected in the serum, which can be a marker of progressive MCD.

LARGE B-CELL LYMPHOMA ARISING IN KSHV-ASSOCIATED MCD

Large B-cell lymphoma arising in KSHV-associated MCD is characterized by a monoclonal proliferation of KSHV-infected lymphoid cells resembling plasmablasts expressing IgM, arising in the setting of MCD (Dupin et al., 2000; Oksenhendler et al., 2002). The small confluent sheets of LANA-1$^+$ plasmablasts are seen in the interfollicular zone of KSHV-associated MCD. This type of lymphoma occurs in the lymph node or spleen with generalized lymphadenitis and/or massive splenomegaly. Plasmablasts show stippled nuclear staining for LANA-1 and cytoplasmic staining for vIL-6, and strongly express cIgM with λ light-chain restriction.

CONCLUSION

Since the discovery of KSHV, 16 years have passed. During the period, some useful diagnostic tools have been developed for pathological examination. Anti-LANA-1 antibody is the most powerful tool for diagnosis of pathological samples of KSHV infection. LANA-1 expression is specific to KSHV infection, because all KSHV-infected cells express LANA-1. Real-time PCR is also a powerful tool for diagnosis. Thus, it is not difficult to diagnose KSHV infection in pathological samples. On the other hand, the pathogenesis, and especially the oncogenesis, of KSHV remain unknown. Although many KSHV-encoded proteins have been characterized and their *in vitro* functions revealed, it is still not clear if KSHV can fully transform or immortalize endothelial cells. It has been shown that LANA-1 plays a central role in KSHV pathogenesis. However, LANA-1 is not enough for KSHV oncogenesis. KSHV-encoded non-transforming proteins may collaborate to establish and maintain appropriate environment for KSHV-infected cells. Further studies should reveal the mechanism of the collaboration by KSHV-encoded proteins.

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