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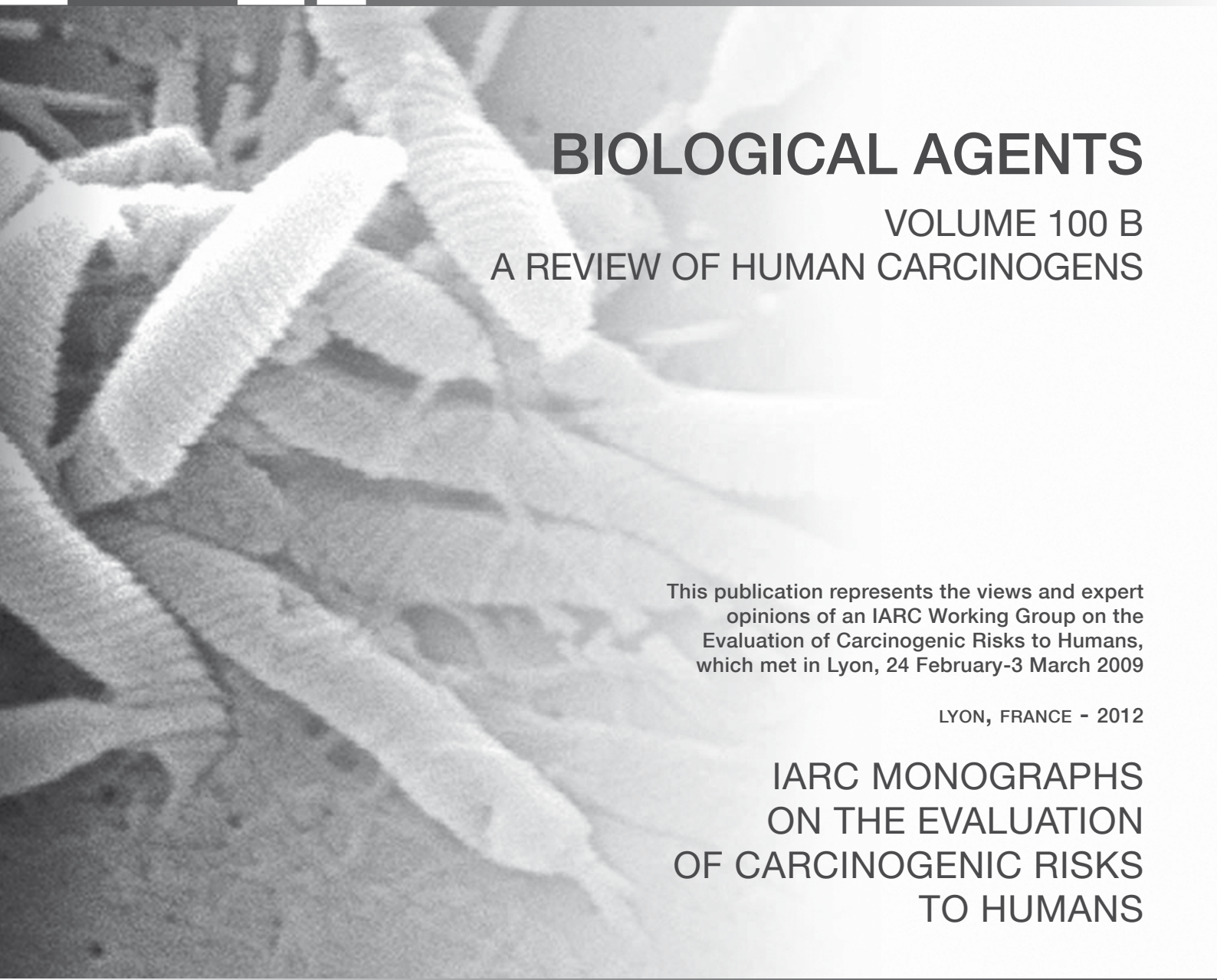

BIOLOGICAL AGENTS

VOLUME 100 B
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 24 February-3 March 2009

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IARC MONOGRAPHS
ON THE EVALUATION
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International Agency for Research on Cancer
World Health Organization

KAPOSI SARCOMA HERPESVIRUS

Kaposi sarcoma herpesvirus was considered by a previous IARC Working Group in 1997 (IARC, 1997). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Taxonomy, structure, and biology

1.1.1 Taxonomy

First detected by Chang *et al.* (1994) in Kaposi sarcomas associated with the acquired immune deficiency syndrome (AIDS) (see IARC, 1996) by representational difference analysis, this virus was termed Kaposi-sarcoma-associated herpesvirus, KSHV. KSHV is also associated with primary effusion lymphoma and some cases of multicentric Castleman disease (see Section 2). In keeping with the systematic nomenclature adopted for all human herpesviruses, the formal designation human herpesvirus 8 (HHV-8) was proposed by the herpesvirus subcommittee of the International Committee on the Taxonomy of Viruses. In this *Monograph*, the term KSHV is used throughout.

On the basis of phylogenetic analyses (Moore *et al.*, 1996a; Russo *et al.*, 1996), KSHV is a gamma-2 herpesvirus (rhadinovirus), and represents the first 'human' member of this group. There are many more gamma-2 herpesvirus species in old and new world non-human primates.

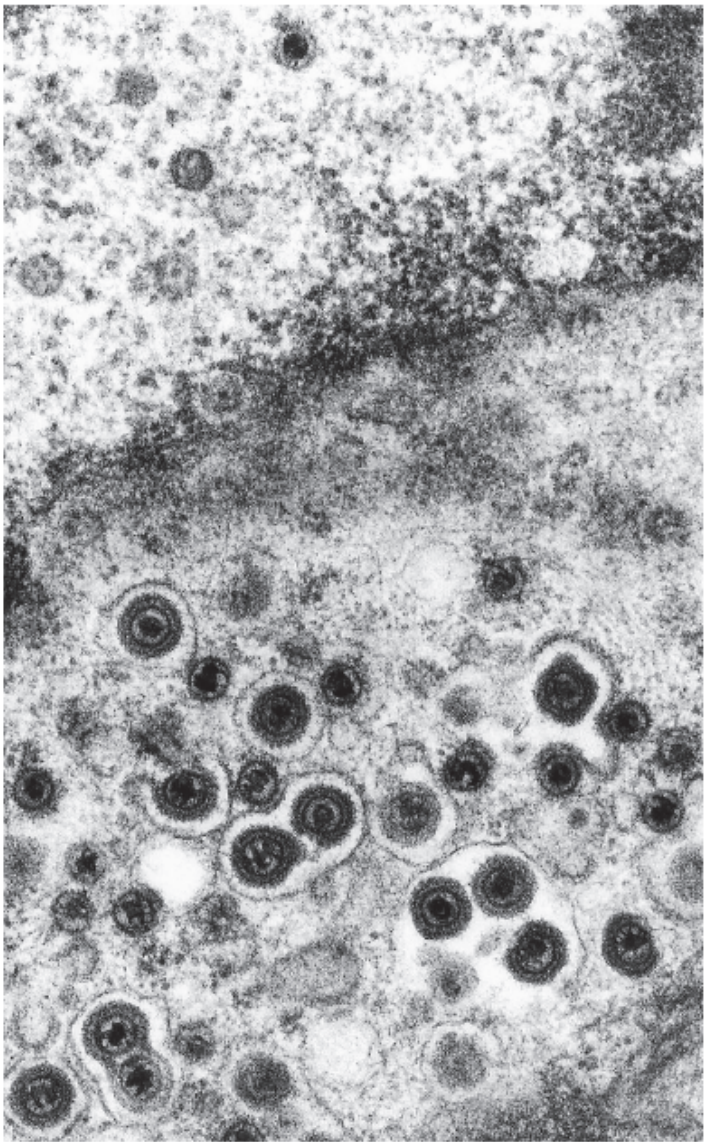
1.1.2 Structure of the virion

KSHV has the typical morphological characteristics of a herpesvirus (Fig. 1.1; Arvanitakis *et al.*, 1996; Renne *et al.*, 1996a; Orenstein *et al.*, 1997) with 100–150 nm particles surrounded by a lipid envelope, and an electron-dense central core (Renne *et al.*, 1996b). Cryo-electron microscopy (Cryo-EM) and Cryo-EM tomography studies suggest that KSHV capsomers are hexamers and pentamers of the major capsid protein (encoded by the open reading frame [ORF] 25), with the small capsid protein (encoded by ORF 65), binding around the tips of both hexons and pentons (Trus *et al.*, 2001; Deng *et al.*, 2008).

1.1.3 Structure of the viral genome

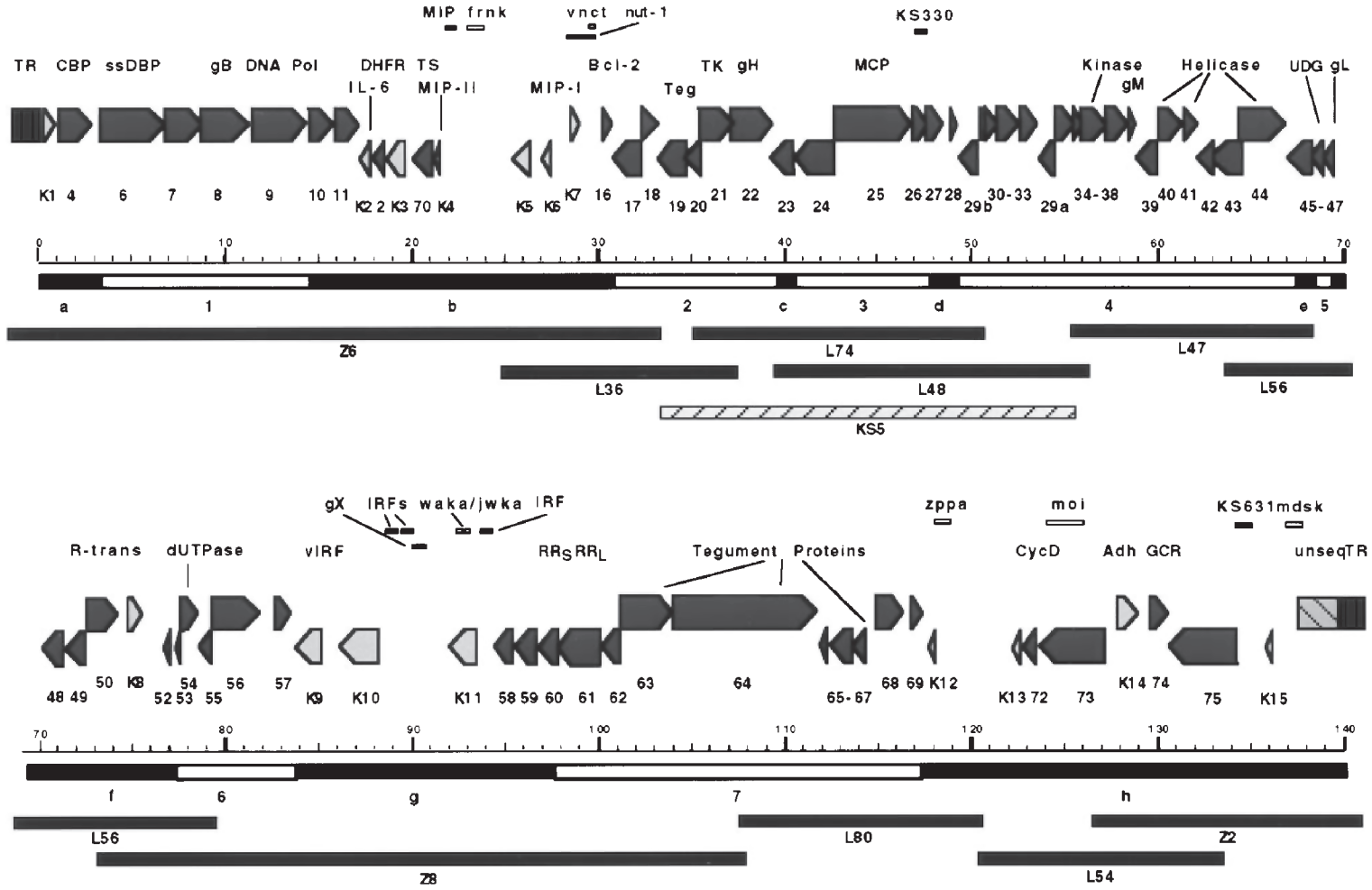
KSHV has a double-stranded DNA genome. The genomic structure of the virus (Russo *et al.*, 1996; Neipel *et al.*, 1997a) is similar to that of other primate rhadinoviruses, e.g. *Herpesvirus saimiri* (Albrecht *et al.*, 1992) or Rhesus Rhadinovirus (Searles *et al.*, 1999; Alexander *et al.*, 2000), with a single, contiguous 140.5-kb-long unique region containing all the identified viral genes (Russo *et al.*, 1996; Neipel *et al.*, 1997a; Fig. 1.2). This region is flanked on either side by a terminal-repeat (TR) region composed of a variable number of repeats of 801-bp length with a high

Fig. 1.1 Electron microscopic view of KSHV capsids in a cross-section of a spleen Kaposi sarcoma



Cytoplasmic viral capsids obtain their lipid outer membrane by budding into cisternae; the electron dense central core represents viral DNA. Original magnification: x53 000.
From Orenstein *et al.* (1997), AIDS 11: F35–F45, "Copyright © 1997 Lippincott-Raven Publishers."

Fig. 1.2 Annotated long unique region and terminal repeats of the KSHV genome



The orientation of identified open reading frames in the long unique region is denoted by the direction of arrows, with *Herpesvirus saimiri* homologous with open reading frames as shaded areas and those not homologous as lighter areas. Seven blocks (numbered) of conserved herpesviral genes with non-conserved interblock regions (lettered) are shown under the kilobase marker. Features and putative coding regions not specifically designated are shown above the open reading frame map. Repeat regions (frnk, vnct, waka/jwka, zppa, moi, mdsk) are shown as light lines, and putative coding regions and other features are not designated as open reading frames are shown as solid lines.
From Russo *et al.* (1996), PNAS 93: 1486–1487, "Copyright (2010) National Academy of Sciences, USA."

G:C (84.5%) content. Due to the variable number of repeat subunits (some of the repeat subunits may be truncated), the overall length of the TR region varies, and with it, the overall size of the KSHV genome. The latter has been calculated to be approximately 165 kb on the basis of studies of the viral genome from productive primary effusion lymphoma cells (Arvanitakis *et al.*, 1996; Renne *et al.*, 1996b), and mapping of the whole genome (Russo *et al.*, 1996).

(a) Terminal-repeat region

The TR region is a conserved feature of herpesviruses, and is involved in the packaging of the viral DNA into new virions during the lytic cycle of replication. Depending on the viral strain, KSHV has approximately 20–30 TR units. A particular feature of the KSHV TR unit is that it contains two binding sites for the KSHV latent nuclear antigen (LANA) and the latent (episomal) origin of replication (Garber *et al.*, 2001; Hu *et al.*, 2002). By binding to multiple TR subunits, LANA tethers circular viral episomes to mitotic chromosomes during mitosis (Ballestas *et al.*, 1999; Barbera *et al.*, 2006). LANA is also required for the replication of viral episomes by recruiting a range of cellular factors involved in DNA replication (see Section 4.1). Currently, the TR region is not known to contain any protein-coding ORFs in contrast to, for example, EBV (Longnecker & Neipel, 2007).

(b) Long unique region

The KSHV 140.5-kb long unique region encodes approximately 90 predicted ORFs (Russo *et al.*, 1996; Neipel *et al.*, 1997a; Fig. 1.2). The ORFs were named according to the corresponding *herpesvirus saimiri* genes with which they share a significant level of sequence similarity. Unique genes that are not homologous with *herpesvirus saimiri* have a K prefix. The long unique region has blocks of genes conserved among all subfamilies of herpesviruses (Chee *et al.*, 1990), which include genes that encode herpesvirus structural proteins and replication enzymes. Between the conserved herpesvirus gene blocks lie blocks of genes that are either found in rhadinoviruses or are unique to KSHV (Russo *et al.*, 1996). Several of these share significant sequence similarity with cellular genes, and were presumably carried away at some point during the evolution of these viruses.

The long unique region also contains genes for untranslated RNAs. Among these is the *PAN/nut-1* transcript, a nuclear untranslated RNA, whose function is not yet clear (Sun *et al.*, 1996; Zhong & Ganem, 1997). In addition, KSHV encodes at least 12 microRNAs, which are generated from one transcript, and located downstream of the *ORFK13/vFLIP* (Cai *et al.*, 2005; Samols *et al.*, 2005).

The probable function of these genes in the virus life cycle and tumour formation is discussed in Section 4.1.

1.1.4 Host range and tropism

Humans are the natural hosts for KSHV. Epidemiological studies indicate that KSHV is more prevalent in subSaharan Africa, several countries of southern Europe, the North African Mediterranean coast, and several countries of South America compared to northern Europe, North America, and Asia (see Section 1.2).

In vivo, KSHV has been detected in endothelial and spindle cells of Kaposi sarcoma lesions, in circulating endothelial cells, primary effusion lymphoma cells, B cells, macrophages, dendritic cells, oropharynx and prostatic glandular epithelium and keratinocytes (Ambroziak *et al.*, 1995; Boshoff *et al.*, 1995; Cesarman *et al.*, 1995a; Moore & Chang, 1995; Corbellino *et al.*, 1996; Li *et al.*, 1996; Sirianni *et al.*, 1997; Staskus *et al.*, 1997; Stürzl *et al.*, 1997; Reed *et al.*, 1998; Pauk *et al.*, 2000).

Of the cell types targeted by KSHV *in vivo*, primary endothelial cells of different differentiation (vascular, lymphatic, endothelial precursor

cells), monocytes, dendritic cells, fibroblasts, epithelial cells and keratinocytes can be infected *in vitro* (Renne *et al.*, 1998; Blackbourn *et al.*, 2000; Cerimele *et al.*, 2000; Wang *et al.*, 2004a; Rappocciolo *et al.*, 2006). It was shown that B cells can only be infected *in vitro* at a specific differentiation stage (Rappocciolo *et al.*, 2006, 2008).

1.1.5 Viral life cycle

KSHV, like all herpesviruses, can establish lifelong latent infections in their human host. Latenly infected cells provide a perpetual reservoir from which progeny viruses can be amplified for dissemination within the host and transmission between hosts. The peripheral blood CD19-positive B cells have been identified as a long-term latency reservoir for KSHV; other cells such as endothelial cells may also be a site for KSHV latency, but they do not appear to provide a long-term latent reservoir for the virus. Nonetheless, infected dermal endothelium spindle cells may release progeny virus that can subsequently infect local keratinocytes and the eccrine epithelium in the tumour. Lytic reactivation from latently KSHV-infected cells that results in the release of progeny virions is a critical pathogenic step in multiple human diseases. In immunocompetent KSHV carriers, the immune system plays an essential role in tempering lytic reactivation of the virus (see Lukac & Yuan, 2007 for a detailed review).

1.2 Epidemiology of infection

In the previous *IARC monograph* (IARC, 1997), preliminary epidemiological data were presented based largely on Polymerase Chain Reaction (PCR) and initial serological studies. Subsequently, substantial additional data have become available with the advent of new serological techniques and large-scale studies.

1.2.1 Prevalence, geographic distribution

(a) Laboratory methods in epidemiological studies of KSHV

Difficulties have arisen in developing reliable serological tests to assess KSHV infection, and the interpretation of some published KSHV prevalence data is therefore challenging. KSHV encodes multiple antigenic proteins that may be expressed in the latent or lytic phase of the virus life cycle (Chandran *et al.*, 1998). The major antigenic proteins are the LANAs encoded by ORF 73, and the lytically expressed K8.1 encoded by ORF 65. First-generation serological assays were developed based on the immunofluorescence of latently infected primary effusion lymphoma cells (Gao *et al.*, 1996; Kedes *et al.*, 1996; Simpson *et al.*, 1996) or primary effusion lymphoma cells induced by treatment with tetradecanoyl phorbol ester acetate (TPA) to produce lytic antigens (Lennette *et al.*, 1996). More recently, enzyme-linked immunosorbent assays (ELISAs) have been developed using recombinant proteins or peptides.

Concordance between assays detecting antibodies to these antigens has improved but remains moderate. Infected subjects may have antibodies to only lytic or latent antigens, and may develop antibody responses to lytic antigens years before they develop antibodies to LANA, and the reverse can also occur (Biggar *et al.*, 2003, Minhas *et al.*, 2008). In addition, antibody titres are very high in Kaposi sarcoma patients but very low in asymptomatic subjects (Biggar *et al.*, 2003). [The Working Group concluded that if the serum samples of Kaposi sarcoma patients are used as "gold standard" positive controls then the sensitivity of an assay is likely to be overestimated. At the other end of the spectrum, antibody levels in asymptomatic subjects are so low that establishing a clear assay cut-off is difficult. For these reasons, current assays for KSHV antibody detection, while suitable for comparisons between populations,

are inadequate for diagnostic purposes in low-risk populations. Comparisons between studies using different assays or even different cut-offs are often problematic.]

(b) *Seroprevalence estimates and geographic distribution*

Despite the difficulties discussed above in estimating the precise prevalence of KSHV, prevalence is in general low (< 10%) in northern Europe, the USA and Asia, elevated in the Mediterranean region (10–30%), and high in subSaharan Africa (> 50%) (Enbom *et al.*, 2002; Dukers & Rezza, 2003). A study of 1000 blood donors in the USA tested by six independent laboratories reported estimates ranging from 0.5–5% (Pellett *et al.*, 2003). More recently, a study of approximately 14000 adults recruited for the National Health and Nutrition Examination survey (NHANES) III, designed to be representative of the general population, estimated KSHV prevalence to be around 7% (Engels *et al.*, 2007). In northern Europe, KSHV is reported to be 2–3% in adults (Simpson *et al.*, 1996; Marcelin *et al.*, 1998; Preiser *et al.*, 2001). Prevalence in Asia is similar to that in the USA and northern Europe. A large international study recently reported a prevalence of 5% for the Republic of Korea, 8–10% for Thailand, and 11–15% for Viet Nam (de Sanjosé *et al.*, 2009).

KSHV prevalence is higher in adults in Mediterranean countries such as Italy than in northern Europe or the USA (Gao *et al.*, 1996; Whitby *et al.*, 1998), with prevalence higher in Southern Italy and in the Po Valley (13–20%) than in most of Northern Italy (Calabrò *et al.*, 1998; Whitby *et al.*, 1998; Cattani *et al.*, 2003; Serraino *et al.*, 2006). The prevalence in Spain is reported to be 3.65% (de Sanjosé *et al.*, 2009), in Greece 7.6% (Zavitsanou *et al.*, 2007), and in Israel 10% (Davidovici *et al.*, 2001). In South America, a high prevalence of KSHV infection is reported in Amerindians but not in the general population (Biggar *et al.*, 2000; Whitby *et al.*, 2004; Cunha *et al.*, 2005).

The prevalence of KSHV in Uganda is 40–50% (Gao *et al.*, 1996; Wawer *et al.*, 2001; Hladik *et al.*, 2003; Newton *et al.*, 2003a). Similar estimates are reported for Kenya (~43%) (Baeten *et al.*, 2002; Lavreys *et al.*, 2003), Zambia (40%) (Klaskala *et al.*, 2005), and the United Republic of Tanzania (~ ≥50%) (Mbulaiteye *et al.*, 2003a). KSHV prevalence appears to be higher in Malawi (54–67%), Botswana (76%), and The Demographic Republic of Congo (82%) (Engels *et al.*, 2000; DeSantis *et al.*, 2002; Whitby *et al.*, 2004).

KSHV prevalence is somewhat lower in South Africa (30%) (Sitas *et al.*, 1999; Dedicoat *et al.*, 2004; Malope *et al.*, 2007), and in West African countries such as Burkino Faso (~12.5%) and Cameroon (~25%) (Volpi *et al.*, 2004; Collenberg *et al.*, 2006). The Gambia had a low incidence of Kaposi sarcoma before and during the AIDS epidemic but has a high KSHV prevalence (~75%) (Ariyoshi *et al.*, 1998). The prevalence of KSHV in Nigeria is intermediate (~45%) (de Sanjosé *et al.*, 2009).

1.2.2 *Transmission and risk factors for infection*

KSHV is primarily transmitted via saliva. In countries where KSHV is highly prevalent, infection occurs during childhood and increases with age (Whitby *et al.*, 2000; Dedicoat *et al.*, 2004; Malope *et al.*, 2007). The peak age of acquisition is generally between 6–10 years (Whitby *et al.*, 2000; Mbulaiteye *et al.*, 2004), and the risk of infection is increased if family members, especially mothers, are infected (Plancoulaine *et al.*, 2000; Dedicoat *et al.*, 2004; Malope *et al.*, 2007; Minhas *et al.*, 2008). Other reported risk factors for infection in childhood include human immunodeficiency virus (HIV) infection (Malope *et al.*, 2007; Minhas *et al.*, 2008), environmental factors such as source of water (Mbulaiteye *et al.*, 2005), and insect bites (Coluzzi *et al.*, 2003). In

the USA, Europe and Australia, KSHV prevalence is elevated in homosexual men, especially those infected by HIV (Martin *et al.*, 1998; Smith *et al.*, 1999; Grulich *et al.*, 2005). There is considerable evidence that the risk of infection with KSHV is associated with the number of sexual partners of an individual, and other sexual risk factors (Martin *et al.*, 1998; Smith *et al.*, 1999; Grulich *et al.*, 2005). It is likely that the transmission of KSHV between homosexual men is also via saliva (Martin, 2003; Martró *et al.*, 2007). KSHV is not generally associated with sexual risk factors in heterosexuals (Smith *et al.*, 1999; Engels *et al.*, 2007; Malope *et al.*, 2008; de Sanjosé *et al.*, 2009).

KSHV can be detected in peripheral blood suggesting that blood-borne transmission is possible. Some studies have suggested that injecting drug use was not associated with a risk of KSHV infection (Renwick *et al.*, 2002; Bernstein *et al.*, 2003), but others have shown an increased risk of KSHV infection in injecting drug users, especially with prolonged use (Cannon *et al.*, 2001; Atkinson *et al.*, 2003). KSHV transmission via blood transfusion is also likely to be rare, but evidence of both risk and actual transmission has been reported (Mbulaiteye *et al.*, 2003b; Dollard *et al.*, 2005; Hladik *et al.*, 2006). KSHV transmission by organ donation has also been reported (Parravicini *et al.*, 1997, Concato *et al.*, 2008).

2. Cancer in Humans

2.1 Kaposi sarcoma

At the time of the previous *IARC Monograph* (IARC, 1997), KSHV was classified as 'probably carcinogenic to humans' (Group 2A) on the basis 'that the evidence was compelling but as yet limited'. Since then, a large number of studies have assessed the association between KSHV and Kaposi sarcoma (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.1.pdf, and Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.2.pdf).

To date, data on the association between KSHV and Kaposi sarcoma come from 22 cohort studies and 80 case–control studies – all show broadly consistent evidence of an association between KSHV infection and Kaposi sarcoma. In most studies, the relative risks for the association between KSHV infection and Kaposi sarcoma are typically greater than 10. Of the 22 cohort studies, conducted in nine countries across three continents, 13 were among cohorts of HIV-infected people and included data on 561 cases. The largest study included 189 cases (Newton *et al.*, 2006). Nine cohorts of transplant recipients yielded a total of 48 cases (Parravicini *et al.*, 1997; Regamey *et al.*, 1998; Francès *et al.*, 1999, 2000; Rabkin *et al.*, 1999; Cattani *et al.*, 2001; Emond *et al.*, 2002; Marcelin *et al.*, 2004; García-Astudillo & Leyva-Cobián, 2006). No data were available from cohort studies on "classical" or "endemic" Kaposi sarcoma; to date, all studies have included only immunosuppressed subjects. Two studies used PCR to identify evidence of KSHV in peripheral blood mononuclear cells (PBMC) (Whitby et al, 1995; Moore *et al.*, 1996b), most studies used serology, and one study used both (Engels *et al.*, 2003). One study demonstrated a statistically significant increasing risk of Kaposi sarcoma with increasing titre of antibodies against KSHV, before diagnosis, both for a lytic and a latent assay (Newton *et al.*, 2006).

Of the 80 case–control studies, nearly half included data on cases not infected by HIV – i.e. "classical," "endemic", and transplant-associated Kaposi sarcoma. A variety of assays were used to detect evidence of infection, including PCR of tumour lesions, semen, prostate tissue, saliva, and bronchial alveolar lavage. Serological studies used assays against lytic or latent antigens, or both. Two studies (Sitas *et al.*, 1999; Newton *et al.*, 2003b) had substantial numbers of Kaposi sarcoma cases among HIV-uninfected

individuals and together with one other study (Albrecht *et al.*, 2004) were able to demonstrate increasing risks of Kaposi sarcoma associated with increasing titres of anti-KSHV antibodies (Brown *et al.*, 2006a, b). In addition, among KSHV-seropositive people, the presence of KSHV DNA in PBMC was associated both with an increased risk of Kaposi sarcoma, and with an increased risk of disease progression (Laney *et al.*, 2007). Broadly, results were consistent across all studies, demonstrating a clear association between infection with KSHV and Kaposi sarcoma.

2.2 Primary effusion lymphoma

Primary effusion lymphoma is a very rare subgroup of B-cell non-Hodgkin lymphomas presenting as pleural, peritoneal, and pericardial (body cavity) lymphomatous effusions. These comprise less than 2% of HIV-related lymphomas (Sullivan *et al.*, 2008). There is already strong evidence that KSHV is a causal agent of primary effusion lymphoma (IARC, 1997). Because of the rarity of primary effusion lymphoma, much of the information comes from case reports, with a few studies that have examined biopsy tissues, aspirates or cell lines. Primary effusion lymphomas were described in HIV-immunosuppressed individuals by Cesarman *et al.* (1995a) in association with KSHV, and by Nador *et al.* (1996) as a distinct disease entity, and almost all occurred in association with HIV (Gaidano *et al.*, 2000). Because of the identification of KSHV in all of the cases presenting as primary lymphomatous effusions in early studies, the presence of this virus has been incorporated as a diagnostic criterion for primary effusion lymphoma. However, it has since been recognized that other lymphoma subtypes such as Burkitt or diffuse large B-cell lymphoma can also present in body cavities, and these lack the presence of KSHV. In addition, some KSHV-positive lymphomas occur as solid tumour masses with or without accompanying effusions. However, KSHV-associated lymphomas have a multitude of morphological and immunophenotypical features that are characteristic, and so, have been grouped as a single clinicopathological entity. Cases without an effusion are considered to be extracavitary variants of primary effusion lymphoma (Said & Cesarman, 2008).

See Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.3.pdf, and Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.4.pdf.

Some primary effusion lymphomas occur in association with post-transplant immunosuppression (Kapelushnik *et al.*, 2001). Many case reports show primary effusion lymphoma to be in association with Kaposi sarcoma or multicentric Castleman disease, both known to be caused by KSHV. Ascoli *et al.* (2001), for example, also identified four patients with multicentric Castleman disease and primary effusion lymphoma, all of which had evidence of KSHV DNA in pleural effusions. In a prospective cohort study of 60 HIV-positive patients, three developed primary effusion lymphoma in association with multicentric Castleman disease and/or Kaposi sarcoma, the latter conditions appear to be risk factors for the development of this disease (Oksenhendler *et al.*, 2002). Komanduri *et al.* (1996) and numerous case reports (e.g. Ascoli *et al.*, 1999a, b) described HIV-positive cases of primary effusion lymphoma that had evidence of KSHV infection. Likewise, four patients with primary effusion lymphoma and five cell lines were all reported to be KSHV-positive (Judde *et al.*, 2000). Boulanger *et al.* (2005) identified 15 HIV-positive patients with primary effusion lymphoma, all of which were KSHV-positive. Of interest, in this study, six primary effusion lymphoma patients had neither Kaposi sarcoma nor multicentric Castleman disease. Asou *et al.* (2000) found KSHV to be present in 21/21 patients with primary effusion lymphoma, compared with 0/139 patients with other AIDS- and non-AIDS-related lymphomas,

and mucosa-associated lymphoid tissue (MALT) lymphomas.

During 1996–2008, a total of 95 subjects were identified in the literature as case reports. The majority of these were KSHV-positive and HIV-positive. Nineteen subjects were KSHV-negative and HIV-negative; these were unusual in that all but three were elderly, seven of these were characterized by having had some form of genetic abnormality, three had cirrhosis (two of those were due to infection with the hepatitis C virus), two had some other idiopathic immunodeficiency, and one had a renal transplant. These cases do not fulfill the diagnostic criteria for primary effusion lymphoma (Said & Cesarman, 2008), and probably represent another form of non-Hodgkin lymphoma involving body cavities. Primary effusion lymphoma has also been reported in people with no obvious immune suppression or HIV infection. See Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.5.pdf.

2.3 Multicentric Castleman disease

Strictly speaking, multicentric Castleman disease is not a cancer, but a rare polyclonal lymphoproliferative disease that can progress to plasmablastic lymphoma (Dupin *et al.*, 2000). In addition, Oksenhendler *et al.* (2002) found that 14/60 HIV-infected patients with multicentric Castleman disease developed non-Hodgkin lymphoma, three of which were primary effusion lymphoma. Several studies have associated multicentric Castleman disease with KSHV. Multicentric Castleman disease was recognized in 1956 (Castleman *et al.*, 1956), but appears to have increased in incidence as a result of the HIV epidemic, although multicentric Castleman disease in association with KSHV has also been documented in HIV-negative patients (Hernández *et al.*, 2005).

Table 2.6 (available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.6.pdf) shows case series that have detected KSHV in patients with multicentric Castleman disease (Soulier *et al.*, 1995; Barozzi *et al.*, 1996; Corbellino *et al.*, 1996; Gessain *et al.*, 1996). Several hospital-based studies have shown an association between KSHV and multicentric Castleman disease, irrespective of the way in which KSHV is detected and of differences in tissue type (Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.7.pdf; Soulier *et al.*, 1995; Parravicini *et al.*, 1997; Bélec *et al.*, 1999a; Asou *et al.*, 2000). For example, Soulier *et al.* (1995) found KSHV to be present in all 14/14 HIV-positive cases and 7/17 HIV-negative cases compared with 1/34 controls. Treatment of three multicentric Castleman disease patients with ganciclovir, an inhibitor of KSHV lytic replication, has been reported to ameliorate multicentric Castleman disease (Casper *et al.*, 2004), while treatment with cidofovir, an inhibitor of KSHV DNA polymerase, was not effective (Corbellino *et al.*, 2001; Berezne *et al.*, 2004).

2.4 Multiple myeloma

A small number of early studies suggested a possible association between KSHV and multiple myeloma (Rettig *et al.*, 1997; Said *et al.*, 1997), but this was not confirmed by subsequent large well designed serology and PCR-based studies (see Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.8.pdf). In addition, the geographic distribution of multiple myeloma is different from that of Kaposi sarcoma and of KSHV, strongly implying different etiologies (Cottoni & Uccini, 1997; Globocan, 2008; Hjalgrim *et al.*, 1998). [The Working Group noted that a map of the global distribution of Kaposi sarcoma was not available from Globocan 2008 because it is only possible to derive estimates for subSaharan African countries.]

Several studies containing a clinical series of patients with multiple myeloma and a comparison group of other hospital patients without *monoclonal gammopathy of undetermined significance* (MGUS, thought to be a precursor of multiple myeloma) or blood donors, have not found an association between markers of KSHV and multiple myeloma (Mackenzie *et al.*, 1997; Marcelin *et al.*, 1997; Masood *et al.*, 1997; Rettig *et al.*, 1997; Whitby *et al.*, 1997; Agbalika *et al.*, 1998; Santarelli *et al.*, 1998; Bélec *et al.*, 1999b, c; Azzi *et al.*, 2001; Beksac *et al.*, 2001; Patel *et al.*, 2001; Santón Roldán *et al.*, 2002; Zhu *et al.*, 2002; Hermouet *et al.*, 2003; Tsai *et al.*, 2005). Rettig *et al.* (1997) reported the presence of KSHV sequences using PCR in all 15 of the patients with multiple myeloma, in 2/8 cases with MGUS, and in 0/26 control patients. [The Working Group noted that the majority of studies are based on series of hospital patients which are compared to a series of hospital patients admitted with several unrelated conditions or to blood donors (or both), and therefore the comparison group may not have been adequate. Most studies were typically small in size and did not adjust for age.]

Some of these studies were also reviewed by Tarte *et al.* (1998, 1999), and many used several serological assays against KSHV LANAs. In two of these studies (Agbalika *et al.*, 1998; Bélec *et al.*, 1999b), 0/25 cases of multiple myeloma was seropositive versus 0/25 in controls. Neither of these studies attempted to account for age (through matching or adjusting the data).

The biological significance of some of the clinical series, especially those using small PCR fragments has been questioned by Zong *et al.* (2007). Four studies (Schönrich *et al.*, 1998; Sitas *et al.*, 1999; Tedeschi *et al.* 2001, 2005) had age-matched controls or were based on a case–control/comparison design (Sitas *et al.*, 1999), or had a case–control study design nested within a cohort (Tedeschi *et al.*, 2001, 2005) (see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100B/100B-04-Table2.9.pdf).

Schönrich *et al.* (1998) found KSHV lytic antibodies were present in 4/99 multiple myeloma patients versus 2/67 controls. Sitas *et al.* (1999) measured the age- and gender-adjusted KSHV immunofluorescence assay seropositivity in 108 black South African incident cancer patients with newly diagnosed multiple myeloma compared with 3185 cancer patients and 85 blood donors. The age- and gender-adjusted KSHV seroprevalence in multiple myeloma patients versus controls was, respectively, 24% versus 32%.

Tedeschi *et al.* (2001) measured the seroprevalence of KSHV in 47 multiple myeloma cases and 224 age-matched controls from a cohort of 20243 men and 18814 women recruited between 1968–72, and followed until the end of 1991 through the Finnish Cancer Registry. Odds ratios (age-adjusted) for KSHV and multiple myeloma were calculated using IFA lytic antibodies (OR, 2.02; 95%CI: 0.94–4.33; latent OR, 10.0; 95%CI: 0.91–110.3), and Western blot confirmation (any one of ORF 65, 73 and K8.1A; OR, 0.89; 95%CI: 0.25–3.25); none of the associations was found to be statistically significant. In another nested case–control study, Tedeschi *et al.* (2005) identified 329 cases of multiple myeloma, and matched these to 1631 controls, matched for age and gender. The cases and controls arose from about 1133000 individuals from several Nordic cohorts who had donated blood samples. Seropositivity was 12% in multiple myeloma subjects versus 15% in control subjects. No association was found between multiple myeloma and KSHV lytic (OR, 0.8; 95%CI: 0.5–1.1), or latent antibody levels (OR, 0.6; 95%CI: 0.1–2.7). [The Working Group noted that after stratifying by detection method (PCR, LANA or lytic antibodies), no significant differences in the percent KSHV positivity were observed between multiple myeloma cases and controls when the Working Group used χ^2 tests for comparison (data not shown).]

2.5 Other cancers

Sitas *et al.* (1999) measured the seroprevalence of KSHV in 16 major cancer types, including Kaposi sarcoma and multiple myeloma. As expected, the seroprevalence of KSHV among people with Kaposi sarcoma was greater than 80%; among people with all other cancers (oral cavity, oesophagus, lung, stomach, liver, colon/rectum, breast, cervix, prostate, non-Hodgkin lymphoma, Hodgkin disease, leukaemia, myeloma, other minor types [where $n < 50$ in each cancer type]), the seroprevalence was similar to the general population (about 20–30%). Several studies have examined the presence of KSHV sequences in various other cancers but the results are inconclusive. These include mesenchymal tumours (1/76 cases KSHV-positive) (Kazakov *et al.*, 2002), and other lymphomas (e.g. Lazzi *et al.*, 1998, 2006; de Sanjosé *et al.*, 2004). A case series was reported suggesting an association with large-cell immunoblastic lymphomas (Hansen *et al.*, 2000), but this has not been confirmed. No associations were found between KSHV and cancer of the prostate in several cohort and case–control studies (Sitas *et al.*, 1999; Huang *et al.*, 2008), however, one case–control study did present a significant inverse association (Sutcliffe *et al.*, 2007). KSHV has not been detected in salivary gland tumours (Atula *et al.*, 1998), despite the fact that KSHV is thought to be transmitted via saliva.

2.6 Kaposi sarcoma and cofactors

Infection with KSHV alone is not sufficient to cause Kaposi sarcoma. The most important cofactor predisposing a KSHV-infected person to Kaposi sarcoma is HIV co-infection or, to a lesser extent, other immunodeficient states such as iatrogenic immune suppression in organ transplant recipients (IARC, 1997). Nonetheless, the incidence of Kaposi sarcoma in specific geographic areas before the HIV epidemic points to a role of as-yet-unknown cofactors in the etiology of this cancer (Dedicoat & Newton, 2003).

2.6.1 Suspected unknown cofactors

Before the HIV epidemic, Kaposi sarcoma had a much greater geographic variation in incidence than most other malignancies. Classic (sporadic) Kaposi sarcoma occurred but was rare in countries around the Mediterranean, particularly in Italy, Greece, and the Middle East, and was almost non-existent elsewhere in Europe and in the USA, except in immigrants from these countries (Grulich *et al.*, 1992; IARC, 1997). In contrast, it represented up to 9% of all cancers in parts of subSaharan Africa, such as Uganda, in both men and women (Oettlé, 1962; D'Oliveira & Torres, 1972; Templeton, 1981; Hutt, 1983; Cook-Mozaffari *et al.*, 1998; Dedicoat & Newton, 2003). KSHV infection is prevalent in many African countries, including places where Kaposi sarcoma was almost unknown before HIV, and is as common in women as in men (Dedicoat & Newton, 2003). However, the incidence of classical Kaposi sarcoma varied markedly across the African continent, primarily affecting men (Cook-Mozaffari *et al.*, 1998).

Several exposures have been suggested as possible cofactors for diseases that might explain the geographic variation in incidence before the HIV epidemic, both in Africa and elsewhere. These include malaria and other parasitic infections (Serraino *et al.*, 2003; Lin *et al.*, 2008); fine volcanic soils, which are posited to cause localized immunosuppression in the lower limbs (Ziegler, 1993); and exposure to specific plants, or "onco-weeds" that might increase viral replication (Whitby *et al.*, 2007). Although the existence of cofactors is not disputed, for none of these is the evidence sufficiently strong to conclude that there is a definite increase in risk.

2.6.2 HIV infection as a strong cofactor

In parts of Africa where Kaposi sarcoma was relatively common even before the era of HIV, the HIV epidemic has led to an explosion in the incidence of the disease (Curado *et al.*, 2007). In the mid-1990s, the incidence of Kaposi sarcoma increased about 20-fold in Uganda, Zimbabwe, and other subSaharan African countries, such that it is now the most common cancer in men, and the second most common in women (Wabinga *et al.*, 1993, 2000; Bassett *et al.*, 1995; Dedicoat & Newton, 2003). As a result of the HIV epidemic, the incidence of Kaposi sarcoma has also increased in countries where it was previously relatively rare, but where KSHV was prevalent. For example, during 1988–96, the incidence of Kaposi sarcoma increased at least 3-fold in South Africa, and has continued to increase as the HIV epidemic grows. Data from Johannesburg, South Africa, show that incidence rates of Kaposi sarcoma have doubled in men, but have increased 7-fold in women, such that the gender ratio of 7:1 in males versus females in 1988 has now declined to only 2:1 (Sitas & Newton, 2001). [The Working Group noted that this is an artefact of Kaposi sarcoma incidence being higher in men.] Therefore, in the presence of HIV infection, the role of other etiological cofactors may be less relevant for the development of Kaposi sarcoma than before the spread of HIV (Dedicoat & Newton, 2003).

2.6.3 Host genetic susceptibility

Host genetic variation has been investigated in the etiology of Kaposi sarcoma. In particular, emphasis has been placed on genes that may be relevant to the modulation of host immunity against KSHV (Brown *et al.*, 2006a, c; Alkharsah *et al.*, 2007), but data in this area remain sparse. More recent evidence suggests that variations in the viral genome itself may also be of relevance, but currently the findings are inconclusive (Mancuso *et al.*, 2008).

3. Cancer in Experimental Animals

In this volume, the Working Group decided not to include a separate section on "Cancer in Experimental Animals" in the *Monographs* on viruses but rather to include description of such studies under Section 4 (below). The reasoning for this decision is explained in the General Remarks.

4. Other Relevant Data

4.1 Transforming capacity of KSHV

Transformation is a multistep process and KSHV infection has been shown to induce most steps along this progression: a) KSHV infection of primary human endothelial cells leads to morphological alteration and reduced growth-factor dependence (Ciufo *et al.*, 2001); b) KSHV infection of immortalized human endothelial cells leads to extended survival, loss of contact inhibition, growth-factor and anchorage independence (Flore *et al.*, 1998; Moses *et al.*, 1999; Wang & Damania, 2008), and the outgrowth of fully tumorigenic clones (An *et al.*, 2006); c) KSHV transforms murine endothelial progenitor cells (Mutlu *et al.*, 2007).

KSHV infection cannot transform mature human B cells in culture (Kliche *et al.*, 1998). However, this may be due to low infectivity and/or the absence of susceptible cell populations under routine culture conditions, which do not support the growth of haematopoietic cells. Yet, KSHV is clearly required for continued survival of primary effusion lymphoma cells in culture (Guasparri *et al.*, 2004; Godfrey *et al.*, 2005)

Individual KSHV proteins exhibit transforming capacity in experimental systems (see Sections 4.2 and 4.3), and in transgenic mice (see Section 4.6).

4.2 Biochemical and biological properties of KSHV proteins

Several latent or lytic viral proteins are involved in the carcinogenesis process of KSHV (see Table 4.1).

Five KSHV proteins (K1/VIP, vGPCR, vIRF-1, Kaposin A, LANA) have been reported to have transforming properties in classical transformation assays, others (vCYC, LANA, KbZIP) have been shown to affect cell-cycle regulation or the survival of tumour cells *in vivo* or *in vitro* (vFLIP, vIL6, vIRF-3). Because only some of these proteins are expressed during latency and in the majority of tumour cells, not only 'direct' transformations (as in classical models of virus-mediated cellular transformation) but also indirect (paracrine) effects are thought to play a role in KSHV-mediated oncogenesis (Ganem, 2007).

4.2.1 Latent KSHV proteins

(a) LANA/ORF 73

LANA, encoded by *ORF 73*, is expressed during latency and represents the most consistently detected viral protein in KSHV-associated tumour cells (Rainbow *et al.*, 1997; Dupin *et al.*, 1999; Katano *et al.*, 2000; Parravicini *et al.*, 2000). LANA is necessary for replicating the episomal viral DNA; it binds to the latent origin of replication in the TR subunits of the viral genome, and works by recruiting a large variety of cellular interaction partners, among them components of the chromosomal replication machinery such as origin recognition complexes (ORCs), but also cellular proteins linked to transcriptional regulation or proliferation control (see Table 4.1; reviewed in Verma *et al.*, 2007).

Of relevance to a possible direct role of LANA in oncogenesis are the observations that LANA: (i) inactivates p53-dependent transcriptional activation (Friborg *et al.*, 1999); (ii) interacts with pRB and enhances oncogenic ras-mediated transformation of rodent fibroblasts (Radkov *et al.*, 2000); (iii) absorbs GSK-3β and thereby reduces the phosphorylation of, thus stabilizing, β-catenin (Fujimuro *et al.*, 2003); (iv) interacts with Brd2/RING3, a chromatin-binding protein and a lymphomagenic member of the BET protein family (Platt *et al.*, 1999; Viejo-Borbolla *et al.*, 2005); (v) causes B-cell hyperplasia and B-cell lymphoma when expressed in transgenic mice (Fakhari *et al.*, 2006).

(b) vCYC/ORF 72

In-situ hybridization studies indicate that the KSHV *CYC/ORF 72* gene is expressed in the majority of tumour cells *in vivo* (Davis *et al.*, 1997), in keeping with its classification as a latent gene. v-CYC represents another candidate KSHV oncoprotein because of its homology to the human Cyclin-D/Prad oncoprotein. In general, cyclin-D proteins (D_1, D_2, D_3) associate with specific cyclin-dependent kinases (CDKs), and these complexes phosphorylate pRB family members (reviewed in Sherr, 1996). An oncogenic cyclin-D homologue is also present in other gammaherpesviruses (reviewed in Neipel *et al.*, 1997). Ectopic expression of the murine herpesvirus 68 (MHV 68) cyclin in T cells causes T-cell lymphomas in transgenic mice (van Dyk *et al.*, 1999).

The mechanism of transformation by KSHV vCYC is most likely novel and unique, because it phosphorylates pRb but, unexpectedly, also histone H1, $p27^{KIP1}$, and Bcl-2 (Chang *et al.*, 1996; Godden-Kent *et al.*, 1997; Li *et al.*, 1997; Ojala *et al.*, 2000). Unlike human cyclin-D, vCYC/CDK6-mediated phosphorylation of pRB is resistant to inhibition by the cyclin-dependent kinase-inhibitors (CDKIs) $p16^{INK4}$, $p21^{CIP1}$, and $p27^{KIP1}$ (Swanton *et al.*, 1997). Moreover, vCYC/CDK6 induces the degradation of $p27^{KIP1}$ (Ellis *et al.*, 1999; Mann *et al.*, 1999).

Table 4.1 Biochemical and biological properties of KSHV proteins

KSHV protein	Homology to human protein	Viral Gene	Function in viral life cycle	Biochemical properties	Latent/ lytic	Involvement in carcinogenesis	References
K1/VIP [a]		*ORF K1*	May increase/ decrease viral reactivation	Activates several intracellular signalling cascades; Induces angiogenic cytokines; Blocks intracellular transport of BCR-complexes to cell surface	Lytic	Transforming properties Angiogenesis Anti-apoptotic activity	Lee *et al.* (1998a, b, 2000), Lagunoff *et al.* (1999, 2001), Prakash *et al.* (2002), Tomlinson & Damania (2004), Wang *et al.* (2004a, 2006)
KCP	Related to a family of mammalian complement regulatory proteins	*ORF 4*	Inhibits complement activation by virions or virus-infected cells	Cofactor for complement factor I; Accelerates the decay of C3 convertases	Lytic		Mullick *et al.* (2003), Spiller *et al.* (2003), Mark *et al.* (2004)
vIL6	Interleukin-6 (IL6) homologue	*ORF K2*	Viral IL6	Induces proliferation of PEL cell lines Induces VEGF Induces STAT3 phosphorylation	Lytic	Tumour cell survival *in vivo* and *in vitro* Angiogenesis Haematopoiesis	Moore *et al.* (1996a), Burger *et al.* (1998), Aoki *et al.* (1999), Aoki & Tosato (1999), Hoischen *et al.* (2000), Kovaleva *et al.* (2006)
K3/MIR-1/ ZMP-B		*ORF K3*	Downmodulates HLA, ICAM-1, B7.2	E3 ubiquitin ligase	Lytic	Immune evasion	Coscoy & Ganem (2000), Ishido *et al.* (2000), Coscoy *et al.* (2001), Cadwell & Coscoy (2005, 2008), Coscoy (2007) (review)
vCCL-2/ vMIP-II	Chemokine homologue related to macrophage inflammatory protein (MIP)-1α	*ORF K4*	Viral chemokine	Agonist for CCR3, CCR5, CCR8; Induces monocyte chemotaxis	Lytic	Angiogenic properties	Boshoff *et al.* (1997), Dairaghi *et al.* (1999), Endres *et al.* (1999), Nakano *et al.* (2003)
vCCL-3/ vMIP-III	Some homology to chemokines TARC and eotaxin	*ORF K4.1*	Viral chemokine	CCR4, XCR1 agonist	Lytic	Angiogenic properties	Nicholas *et al.* (1997), Stine *et al.* (2000), Lüttichau *et al.* (2007)
K5/MIR-2	Part of a family of membrane-bound-E3-ubiquitin ligases	*ORF K5*	Downmodulates HLA-A, HLA-B, ICAM-1, CD86, CD1d	E3 ubiquitin ligase	Lytic	Immune evasion	Ishido *et al.* (2000), Sanchez *et al.* (2002), Coscoy (2007)

Table 4.1 (continued)

KSHV protein	Homology to human protein	Viral Gene	Function in viral life cycle	Biochemical properties	Latent/ lytic	Involvement in carcinogenesis	References
vCCL-1/ vMIP-I	Chemokine homologue related to macrophage inflammatory protein (MIP)-1α	*ORF K6*	Viral chemokine	CCR8 agonist; Induces monocyte chemotaxis (VEGF production)	Lytic	Angiogenic properties Anti-apoptotic activity	Nicholas *et al.* (1997), Boshoff *et al.* (1997), Nakano *et al.* (2003)
K7/ vIAP	Structurally related to a splice variant of survivin	*ORF K7*	Apoptosis inhibitor	Binds to and inhibits several proteins involved in apoptosis (see Table 4.2) Induces degradation of IkB, p53, vGCR	Lytic	Anti-apoptotic activity	Feng *et al.* (2002, 2004, 2008), Wang *et al.* (2002)
vBCL-2	Bcl-2 homologue	*ORF 16*	Viral Bcl-2	Heterodimerizes with human Bcl-2	Lytic	Anti-apoptotic activity	Sarid *et al.* (1997)
ORF 36		*ORF 36*	Viral Cdk2-like kinase	Phosphorylates K-bZIP; Activates JNK pathway	Lytic		Polson *et al.* (2001), Hamza *et al.* (2004), Izumiya *et al.* (2007)
ORF 45		*ORF 45*	Virion protein important for lytic replication Inhibits virus-mediated induction of type 1 interferon	Binds to and inhibits phosphorylation of IRF-7	Lytic	Viron infectivity Immune evasion	Zhu *et al.* (2002a, 2006), Zhu & Yuan (2003)
K-RTA		*ORF 50*	Immediate-early transactivator Ubiquitin E3 ligase	Binds to and activates several lytic viral promoters directly or by interacting with RBPJk Promotes ubiquitination and degradation of IRF7 Represses p53	Lytic	Reactivation of lytic viral replication from latency Immune evasion Anti-apoptotic activity	Sun *et al.* (1998), Gradoville *et al.* (2000), Gwack *et al.* (2001), Lukac *et al.* (2001), Liang & Ganem (2003), Yu *et al.* (2005)
K-bZIP		*ORF K8*	Modulates cell cycle and lytic reactivation	EBV Zta homologue; Binds to lytic replication origin; Binds to, antagonizes, and recruits p53 to ND10/PML bodies; Inhibits G1/S transition; Co-regulator of K-RTA	Lytic	Deregulation of cell cycle	Lin *et al.* (1999, 2003), Park *et al.* (2000), Katano *et al.* (2001), Izumiya *et al.* (2003a, b)

Table 4.1 (continued)

KSHV protein	Homology to human protein	Viral Gene	Function in viral life cycle	Biochemical properties	Latent/ lytic	Involvement in carcinogenesis	References
ORF 57/ MTA		*ORF 57*	Exports intronless viral RNAs from nucleus and promotes their translation; Required for the formation of viral progeny	Binds to intronless viral mRNA; Recruits hTREX complex	Lytic		Malik *et al.* (2004), Nishimura *et al.* (2004), Majerciak *et al.* (2007), Boyne *et al.* (2008)
vIRF-1	Interferon regulatory factor homologue	*ORF K9*	Modulates viral interferon responses	Prevents IRF-3-mediated transcription Inhibits p53-transcriptional activity and prevents p53-dependent apoptosis	Lytic	Transformation of rodent fibroblasts Immune evasion Anti-apoptotic activity	Gao *et al.* (1997), Burýsek *et al.* (1999), Lin *et al.* (2001), Nakamura *et al.* (2001), Seo *et al.* (2001)
vIRF-4	Interferon regulatory factor homologue	*ORF K10*		No functional data available	Lytic		Offermann (2007) (review)
vIRF3/ LANA-2	Interferon regulatory factor homologue	*ORF K10.5*	Modulates viral interferon responses	Modulates p53 function; Activates IRF-3, IRF-7, c-myc; Inhibits IRF-5	Lytic in endothelial cells; latent in B-cells	Anti- apoptotic activity Immune evasion Cell survival	Rivas *et al.* (2001), Cunningham *et al.* (2003), Lubyova *et al.* (2004, 2007), Wies *et al.* (2008, 2009)
vIRF-2	Interferon factor homologue	*ORF K11*		Inhibits interferon induction; Inhibits induction of CD95L	Lytic	Immune evasion Anti-apoptotic activity	Burýsek & Pitha (2001),.Kirchhoff *et al.* (2002), Fuld *et al.* (2006)
Kaposin A[a]		*ORF K12*		Interacts with cytohesin-1	Latent/ lytic	Transforming properties in cultured cells	Zhong *et al.* (1996), Muralidhar *et al.* (1998),.Sadler *et al.* (1999), Kliche *et al.* (2001), Tomkowicz *et al.* (2005)
Kaposin B[a]		Alternative reading frame in *ORF K12* mRNA	Modulation of cytokine mRNAs regulated by the p38 pathway	Modulates p38/MK2	Latent/ lytic		Sadler *et al.* (1999), McCormick & Ganem (2005, 2006)

Table 4.1 (continued)

KSHV protein	Homology to human protein	Viral Gene	Function in viral life cycle	Biochemical properties	Latent/ lytic	Involvement in carcinogenesis	References
miRs			Viral microRNAs; Regulation of cellular genes (e.g. genes involved in B-cell differentiation)	miRK-11 regulates similar genes as cellular miR-155	Latent	Potential involvement in: Angiogenesis Immune modulation Anti-apoptotic activity	Cai et.al.2005), Pfeffer *et al.*(2005), Samols *et al.* (2005, 2007), Grundhoff *et al.* (2006), Skalsky *et al.* (2007), Gottwein *et al.* (2007)
vFLIP	Homologue of FLICE (caspase-8)-inhibitory proteins	*ORF K13/ ORF 71*	Viral persistence; Spindle cell formation and lymphomagenesis; Inhibits lytic viral replication	Activates NF-κB; Inhibits CD95/Fas-induced apoptosis, anoikis, superoxide-induced cell death; Modulates MHC-I expression	Latent	Cell survival Anti-apoptotic activity Immune evasion	Keller *et al.* (2000), Grundhoff & Ganem (2001), An *et al.* (2003), Field *et al.* (2003), Sun *et al.* (2003), Guasparri *et al.* (2004, 2006), Grossmann *et al.* (2006), Lagos *et al.* (2007), .Matta *et al.* (2007), Ye *et al.* (2008), Efklidou *et al.* (2008), Thurau *et al.* (2009)
vCyclin/ vCYC	D-type cyclin homologue	*ORF 72*	Viral cyclin; Strongly activates CDK6 protein kinase activity	Phosphorylates H1, pRB, BCL-2, $p27^{KIP1}$ in tandem with CDK6	Latent	Deregulation of cell cycle	Chang *et al.* (1996), Godden-Kent *et al.* (1997), Li *et al.* (1997), Swanton *et al.* (1997), Ellis *et al.* (1999), Mann *et al.* (1999), Ojala *et al.* (2000), Sarek *et al.* (2006), Koopal *et al.* (2007)

Table 4.1 (continued)

KSHV protein	Homology to human protein	Viral Gene	Function in viral life cycle	Biochemical properties	Latent/ lytic	Involvement in carcinogenesis	References
LANA		*ORF 73*	Replication and maintenance of latent viral episome; Partition of episomes to daughter cells	Interacts with histones, p53, pRB, BET proteins, GSK-3β and others; Induces S-phase entry Activates hTERT transcription; Recruits origin-binding proteins	Latent	Anti-apoptic activity Cell survival Deregulation of cell cycle Transforming properties in cells Tumorigenicity in mice	Rainbow *et al.* (1997), Ballestas *et al.* (1999), Friborg *et al.* (1999), Platt *et al.* (1999), Radkov *et al.* (2000), Ballestas & Kaye (2001), Hu *et al.* (2002), Fujimuro *et al.* (2003), Watanabe *et al.* (2003), Verma *et al.* (2004), Hu & Renne (2005), Viejo-Borbolla *et al.* (2005), Fakhari *et al.* (2006), Ottinger *et al.* (2006)
vOX2	OX2 homologue	*ORF K14*	Modulates inflammatory and T-cell responses	Activates or downregulates myeloid lineage cells in a CD200-like manner	Lytic		Chung *et al.* (2002), Foster-Cuevas *et al.* (2004)
vGCR	Homologue of G-protein-coupled receptor	*ORF 74*	Stimulates cellular proliferation	Activates Akt, MEK/Erk, JNK, p38; Induces angiogenic cytokines	Lytic	Transforming properties in cells Tumorigenicity in mice Angiogenesis Anti-apoptotic activity	Arvanitakis *et al.* (1997), Bais *et al.* (1998), Yang *et al.* (2000), Holst *et al.* (2001), Montaner *et al.* (2001, 2003), Guo *et al.* (2003), Mutlu *et al.* (2007), Nicholas (2007) (review)
K15 protein[a]		*ORF K15*	Recruits endothelial cells to infected cells	Activates NF-κB, MEK/Erk; Induces inflammatory cytokines; Interacts with proteins involved in signal transduction (e.g. TRAFs 1, 2, 3), with members of src family of PTK, and with an apoptotic regulatory protein HAX-1	Lytic (possibly latent in B-cells)	Possibly anti-apoptotic activity Possibly angiogenesis	Glenn *et al.* (1999), Choi *et al.* (2000), Sharp *et al.* (2002), Brinkmann *et al.* (2003, 2007), Wang *et al.* (2007)

[a] protein unique to KSHV
Compiled by the Working Group

(c) vFLIP/ORF 71

vFLIP/ORF 71 is transcribed from the LANA promoter, and translated from an internal ribosome entry site located within the v-cyclin coding region (Grundhoff & Ganem, 2001; Low *et al.*, 2001). It is therefore thought to be expressed during latency and in all tumour cells. The vFLIP protein is an adhesion molecule, a homologue of cellular FLICE (caspase-8)-inhibitory protein (FLIP) (Hu *et al.*, 1997). It inhibits CD95/FAS-induced apoptosis *in vitro* by blocking caspase-3, -8 and -9 (Djerbi *et al.*, 1999).

vFLIP directly binds IKKγ and TRAF2; this leads to a constitutive activation of NF-κB signalling (Field *et al.*, 2003; Guasparri *et al.*, 2006). In addition, vFLIP induces MHC-I expression through NF-κB in KSHV-infected lymphatic endothelial cells (Lagos *et al.*, 2007), which underscores the physiological importance of the vFLIP–NF-κB interaction. Moreover, vFLIP transgenic mice develop lymphoma (Chugh *et al.*, 2005). Eliminating either vFLIP or NF-κB activity from primary effusion lymphoma cells induces apoptosis (Keller *et al.*, 2000; Guasparri *et al.*, 2004), demonstrating that this pathway is essential for lymphomagenesis.

(d) Kaposin A/ORF K12

The many transcripts spanning the predicted *K12* ORF (originally called T0.7) are translated in different reading frames, giving rise to the proteins kaposin A, B, C (Zhong *et al.*, 1996; Sadler *et al.*, 1999). In addition, a long transcript extending through *ORF K12* represents the precursor RNA for the KSHV microRNAs (Cai *et al.*, 2005; Pfeffer *et al.*, 2005; Samols *et al.*, 2005). One of these microRNAs, miRK-10, is located within the kaposin A sequence. These transcripts are expressed in all Kaposi sarcoma spindle cells (Staskus *et al.*, 1997; Stürzl *et al.*, 1997), and increase after activation of the lytic replication cycle.

Muralidhar *et al.* (1998) reported that transfection of the kaposin A reading frame into Rat-3 cells induced focus formation, and that these cell lines were tumorigenic in nude mice. There is some discussion as to whether this is due to the kaposin A protein or the miR-K10 located within its sequence. Kaposin A interacts directly with Cytohesin-1, a guanine nucleotide exchange factor for ARF GTPases, and a regulator of integrin-mediated cell adhesion. It was shown that the transformed cellular phenotype induced by Kaposin A in tissue culture could be reversed by a functionally dead Cytohesin-1 mutant (Kliche *et al.*, 2001).

(e) vIRF-3/LANA-2

vIRF-3, one of the viral homologues of interferon regulatory factors, is constitutively expressed in latently KSHV-infected cells, and its expression appears to be tissue specific. vIRF-3 is indeed detected in nearly all primary effusion lymphoma cells and KSHV-associated Castleman disease cells (both of B-lymphocyte origin), but is not expressed in Kaposi sarcoma tumours (endothelial origin) (Rivas *et al.*, 2001).

vIRF-3 binds to and antagonizes p53, and affects the regulation of the interferon response (see Table 4.1).

Knockdown of vIRF-3 in primary effusion lymphoma cells has been shown to induce apoptosis, suggesting that vIRF-3 is required for the survival of KHSV-infected B cells (Wies *et al.*, 2008).

4.2.2 Lytic KSHV proteins

(a) K1/VIP (variable, ITAM-containing protein)

K1/VIP is a viral type I transmembrane protein, featuring two hypervariable domains in its extracellular region, and an immunoglobulin transactivation motif (ITAM) in its C-terminal, cytoplasmic region (Lee *et al.*, 1998b). The K1 protein is expressed during the lytic (productive) replication cycle (Jenner *et al.*,

2001; Paulose-Murphy *et al.*, 2001; Nakamura *et al.*, 2003). Wang *et al.* (2006) reported that, while expression of K1 is not a consistent feature of Kaposi sarcoma, some Kaposi sarcoma biopsies show a marked K1-expression both at the transcript and protein level. K1-expression was also documented by immunohistochemistry on a small subpopulation of mantle zone lymphocytes of KSHV-positive multicentric Castleman disease, and in primary effusion lymphoma cell lines (Lee *et al.*, 2003).

Lee *et al.* (1998a) showed that transfection of a K1-expression vector into rodent fibroblasts induced focus formation, and that K1-transfectants induced lymphoma in the common marmoset. Prakash *et al.* (2002) reported the emergence of sarcomatoid tumours and plasmablastic lymphoma in transgenic mice expressing the K1 protein under the control of an SV40 promoter. These mice showed an increased expression of bFGF; in transgenic B cells, a constitutive activation of NF-κB and increased c-Lyn activity was noted. Wang *et al.* (2006) showed that retroviral transduction of primary endothelial cells extended their life span.

K1 activates several intracellular signalling cascades leading to increased Ca-influx, increased phosphorylation of Syk, Vav, Cbl, and the p85 subunit of PI3K, increased NF-κB activity, and activation of NFAT and AP1 (Lee *et al.*, 1998b; Lagunoff *et al.*, 1999, 2001). The activation of PI3K leads to the activation of AKT by K1 (Tomlinson & Damania, 2004). K1 induces the expression of angiogenic cytokines, including vascular endothelial growth factor (VEGF), and may therefore play a paracrine role in the pathogenesis of Kaposi sarcoma or primary effusion lymphoma (Wang *et al.*, 2004a, 2006).

(b) vIRF-1/ORF K9

vIRF-1 belongs to a group of four viral homologues of interferon regulatory factors (Russo *et al.*, 1996; Cunningham *et al.*, 2003). Stable vIRF-1 transfectants in murine NIH 3T3 cells show signs of transformation (loss of contact inhibition, growth in soft agar), and cause tumours in nude mice (Gao *et al.*, 1997). The main function of vIRF-1 appears to be the inhibition of interferon-β-regulated genes such as $p21^{CIP1}$ (Gao *et al.*, 1997); it also inhibits the induction phase of the interferon response by binding to cellular IRFs (IRF-3, IRF-7), and to the transcriptional co-activators p300 and CBP, and inhibits the formation of functional IRF-3/CBP/p300 complexes and the induction of interferon β transcription (Gao *et al.*, 1997; Burýsek *et al.*, 1999; Seo *et al.*, 2000; Lin *et al.*, 2001). Unlike cellular IRFs, vIRF-1 does not bind directly to cellular DNA.

vIRF-1 is expressed during the lytic (productive) replication in tissue culture and is directly transactivated by K-RTA, the central regulator of the viral lytic programme (Gao *et al.*, 1997; Chen *et al.*, 2000).

(c) vGPCR /ORF 74

ORF 74 encodes a homologue of a G-protein-coupled chemokine receptor, and is constitutively active (reviewed in Nicholas, 2007). It activates a broad range of signalling pathways, including MEK/Erk, JNK, p38, Akt, NFAT, CREB, NF-κB, AP-1, and HIF-1α; these are relevant to the promotion of cell proliferation, cell survival, and angiogenic responses via cytokine gene induction (reviewed in Nicholas, 2007; Hartmann, 2008). Although constitutive, the activity of vGPCR can be modulated both positively and negatively by several cellular chemokines (Groα, IL8, IP-10, SDF-1α), and one viral (vCCL-2) chemokine (reviewed in Hartmann, 2008).

Multiple lines of evidence point to a role of vGPCR in KSHV-induced neoplasia, in particular Kaposi sarcoma. Early studies showed the proliferation-enhancing, constitutive signalling, and transforming properties of vGPCR (Arvanitakis *et al.*, 1997; Bais *et al.*, 1998). Subsequently, vGPCR was shown to cause Kaposi-sarcoma-like tumours in transgenic mice (Yang *et al.*,

2000). In this model, vGPCR was only expressed in a few scattered cells, consistent with a paracrine model involving secretion of angiogenic cytokines (Holst *et al.*, 2001; Guo *et al.*, 2003; Montaner *et al.*, 2003).

In a xenograft model, vGPCR involving a KSHV-transfected murine endothelial cell line was found to be required for tumorigenicity (Mutlu *et al.*, 2007). The relevance of these results to KSHV-associated tumours in humans remains to be determined.

4.2.3 Genomic instability

Evidence of genomic instability has been noted in primary effusion lymphoma cells (microsatellite instability, chromosomal imbalances) (Gaidano *et al.*, 1997; Nair *et al.*, 2006), and late Kaposi sarcoma (Pyakurel *et al.*, 2006). Experimentally, genomic instability has been noted in KSHV-infected primary endothelial cells (Pan *et al.*, 2004), as well as in cell lines stably transfected with LANA (Si & Robertson, 2006), and vCYC-transgenic mice (Verschuren *et al.*, 2004). Abnormal chromosome segregation in KSHV-infected cells was shown to be the consequence of nucleophosmin (NPM1) phosphorylation by CDK6 in concert with vCYC (Cuomo *et al.*, 2008).

4.2.4 DNA-damage response

Transduction of vCYC into primary endothelial cells by a retroviral vector induces a DNA damage response, resulting in the increased phosphorylation of γH2AX (a variant form of histone H2A), which is an early response to DNA double-strand breaks. Increase of γH2AX phosphorylation was also shown in KSHV-infected primary endothelial cells, albeit only after 2 weeks of culture (in spite of vCYC being expressed early on) (Koopal *et al.*, 2007). Other KSHV proteins might therefore interfere with the triggering of the DNA-damage response.

Shin *et al.* (2006) reported that vIRF-1 prevents the DNA-damage response and γH2AX and p53 phosphorylation by binding to and inhibiting ATM kinase, thereby promoting p53 turnover. As noted above, vIRF-1 and LANA interact with p53 and antagonize the transcription of p53-dependent cellular genes, including $p21^{CIP1}$ (Gao *et al.*, 1997; Friborg *et al.*, 1999). In KSHV-infected primary effusion lymphoma cells, vIRF-3 also binds to p53 and inhibits the activation of the p53 promoter (Rivas *et al.*, 2001). In primary effusion lymphoma cells, LANA, p53 and Hdm2 form a trimeric complex (Sarek *et al.*, 2007), and the restoration of the p53 function by treatment with an inhibitor of the p53-Hdm2 interaction – Nutlin-3a – induces apoptosis in primary effusion lymphoma cells (Petre *et al.*, 2007; Sarek *et al.*, 2007).

Most reports have concluded that the inhibition of p53-activated cellular genes by LANA, vIRF-1, and vIRF-3 involves other mechanisms than the degradation or increased turnover of p53. However, one report showed that the recruitment of the Cul5-Elongin BC E3 ligase complex by LANA resulted in the degradation of p53 (Cai *et al.*, 2006).

4.2.5 Cell proliferation and differentiation

KSHV-infected primary endothelial cells undergo spindle cell formation, which express markers of the lymphatic endothelium. Gene expression array studies have shown that KSHV can alter the transcriptome profile of vascular endothelial cells towards a profile that is typical for lymphatic endothelial cells (Carroll *et al.*, 2004; Hong *et al.*, 2004; Wang *et al.*, 2004b). This involves the activation of Prox-1, a transcription factor determining lymphatic endothelial cell differentiation, followed by the increased expression of podoplanin and VEGFR-3 – markers for the lymphatic endothelial cell lineage (Carroll *et al.*, 2004; Hong *et al.*, 2004). The signalling pathways gp130 (the β-chain of the IL6 receptor

used by vIL6) as well as PI3K/Akt and JAK2/STAT3 have been reported to be involved in the induction of Prox-1 in KSHV-infected endothelial cells (Morris *et al.*, 2008).

These data raise the possibility that KSHV infects blood or circulating endothelial cells, and drives them to differentiate into the lymphatic endothelium as they become spindle cells. This may be of major importance to Kaposi sarcoma tumour formation (Morris *et al.*, 2008).

The adoption of a spindle morphology in KSHV-infected cells is thought to be due to vFLIP, a homologue of cellular FLIPs, and potent NF-κB inducer; vFLIP is expressed in latently infected endothelial cells, and NF-κB activation appears to be required for the formation of spindle cells (Grossmann *et al.*, 2006; Sun *et al.*, 2006). vFLIP is also required essentially for primary effusion lymphoma cell survival (see Section 4.2.1).

The viral IL6 homologue, vIL6, is expressed *in vivo* in a subpopulation of primary effusion lymphoma cells and in many KSHV-infected B cells in multicentric Castleman disease lymphoid follicles (Moore *et al.*, 1996c; Katano *et al.*, 2000; Parravicini *et al.*, 2000). It induces proliferation, angiogenesis, and haematopoesis in IL6-dependent cell lineages (Burger *et al.*, 1998; Aoki *et al.*, 1999; Hoischen *et al.*, 2000), and serves as an essential autocrine factor in primary effusion lymphoma cell lines (Jones *et al.*, 1999). It also induces VEGF, which has been implicated in the pathogenesis of primary effusion lymphoma and of Kaposi sarcoma (Aoki & Tosato, 1999). A single-chain antibody to vIL6, blocking its interaction with the IL6 receptor complex, was found to inhibit the proliferation of a primary effusion lymphoma cell line and to inhibit vIL6-induced STAT 3 phosphorylation in vIL6-transfected cells (Kovaleva *et al.*, 2006). Therefore, vIL6 may contribute to primary effusion lymphoma cell proliferation and to the angiogenesis noted in patients with this lymphoma.

Also, the viral D-type cyclin homologue vCYC and LANA each contribute to cell proliferation (see Section 4.2.1)

One of the viral latent transcripts in primary effusion lymphoma cells, miRNA-K12–11, has been found to target the same cellular microRNAs as miRNA-155, a cellular microRNA regulating the germinal centre reaction during B-cell maturation (Gottwein *et al.*, 2007; Skalsky *et al.*, 2007; Thai *et al.*, 2007). Both miRNA-K12-11 and miR-155 downregulate several pro-apoptotic cellular genes (see Table 4.2). miRNA-K12–11 may therefore be involved in blocking terminal B-cell differentiation that contributes to the plasmablastic phenotype of primary effusion lymphoma cells or play a role in the protection of primary effusion lymphoma cells against apoptosis.

These findings highlight how KSHV can affect the differentiation of endothelial cells and of B cells.

vIRF3, an interferon regulation factor homologue, is required for primary effusion lymphoma cell survival (Wies *et al.*, 2008).

Ablation of the human cytokines IL-6, IL-10, and VEGF or of VEGFR inhibits the growth of primary effusion lymphoma and Kaposi sarcoma (Masood *et al.*, 1997; Nakamura *et al.*, 1997; Aoki & Tosato, 1999; Arora *et al.*, 1999; Jones *et al.*, 1999; Sin *et al.*, 2007). IFN-α inhibits KSHV reactivation and Kaposi sarcoma tumour growth (Krown *et al.*, 1986; Chang *et al.*, 2000).

4.2.6 Apoptosis

Several KSHV proteins have been shown to protect against apoptosis when transfected individually. Among them are some of the proteins already discussed above, as well as a viral homologue of cellular Bcl2. Table 4.2 shows a summary of their mode of actions.

Table 4.2 Mode of action of KSHV proteins involved in the protection against apoptosis

KSHV protein	Mode of action	References
K1/VIP	Activation of PI3K/Akt; Inhibition of FKHR-mediated apoptosis; Inhibition of Fas-induced apoptosis	Tomlinson & Damania (2004), Wang *et al.* (2004a), Uddin *et al.* (2005),
vBcl-2	Inhibition of Bax-mediated apoptosis; Selective interaction with BH3-only proteins	Cheng *et al.* (1997), Sarid *et al.* (1997), Flanagan & Letai (2008)
vCCL-1/vMIP-I; vCCL-2/vMIP-II	VEGF-independent anti-apoptotic effect	Liu *et al.* (2001)
K7/vIAP	Inhibition of apoptosis by binding to Bcl-2 and caspase-3; Promotes p53 and IκB degradation by interacting with Ubiquilin/PLIC1; Binds to cellular CAML (calcium-modulating cyclophilin ligand); Increases cytosolic Ca^{2+} response to an apoptotic stimulus	Feng et al. (2002, 2004), Wang *et al.* (2002)
K-RTA	Represses p53-dependent transcription and apoptosis through interaction with CBP	Gwack *et al.* (2001)
vIRF-1	Degradation of p53 by binding to p53 and ATM; Inhibits ATM-mediated phosphorylation of p53 on serine 15; Interacts with GRIM-19 and inhibits interferon or retinoic-acid-induced apoptosis; Inhibits induction of CD95L	Gao *et al.* (1997), Nakamura *et al.* (2001), Seo *et al.* (2001, 2002), Kirchhoff *et al.* (2002), Shin *et al.* (2006)
vIRF-2	Inhibits induction of CD95L; Binds to and inhibits the activation of the IFN-induced ds-RNA-activated kinase (PKR)	Burýsek & Pitha (2001), Kirchhoff *et al.* (2002)
vIRF-3/LANA-2	Inhibits apoptosis in PEL cells; Binds to p53 and inhibits p53-induced transcription and apoptosis; Inhibits apoptosis triggered by PKR	Rivas *et al.* (2001), Esteban *et al.* (2003), Wies *et al.* (2008)
miRNA K12–11	Downregulation of proapoptotic cellular genes, e.g. LDOC1, Bim, BCLAF1 (Bcl2-associated transcription factor 1), BAZF (NF-κB regulator)	Gottwein *et al.* (2007), Skalsky *et al.* (2007)
LANA	Inhibits p53-induced apoptosis; Counteracts pro-apoptotic effects of simultaneously expressed vCyc; Stabilizes and activates c-Myc	Friborg *et al.* (1999), Curreli *et al.* (2005), Bubman *et al.* (2007), Liu *et al.* (2007a), Petre *et al.* (2007), Sarek *et al.* (2007), Cuomo *et al.* (2008)
vFLIP	Binds to FLICE complex; Inhibits CD95/Fas-induced apoptosis; Persistent activation of NF-κB	Thome *et al.* (1997), Chaudhary *et al.* (1999), Djerbi *et al.* (1999), Stürzl *et al.* (1999), Liu *et al.* (2002), An *et al.* (2003), Field *et al.* (2003), Sun *et al.* (2003), Guasparri *et al.* (2004), Godfrey *et al.* (2005)
vGCR	Promotes endothelial cell survival by activating PI3K/Akt pathway	Montaner *et al.* (2001)
K15	Interacts with HAX-1 (an anti-apoptotic regulatory protein	Sharp *et al.* (2002)

FLICE, (FADD [Fas-associated death domain]-like IL-1β-converting enzyme); FLIPs, FLICE-inhibitory proteins
Compiled by the Working Group

4.3 Evidence for a role of KSHV in malignant conversion

4.3.1 Kaposi sarcoma

(a) Requirement of KSHV expression for cell growth invasion

In vitro, KSHV alters the transcriptional programme in infected primary endothelial cells, leading to a redifferentiation of vascular endothelial cells into lymphatic endothelial cells; this results in the formation of spindle cells that are similar to spindle cells in Kaposi sarcoma (see Section 4.2.4). These infected cells, however, cannot be maintained in long-term culture as they show evidence of spontaneous lytic reactivation (Ciufo *et al.*, 2001; Lagunoff *et al.*, 2002).

Owing to a lack of an easily tractable *in vivo* model, not many published studies have addressed the question of whether or not KSHV is required for cell growth and invasion *in vivo*. Mutlu *et al.* (2007) reported that transfection of a bacterial artificial chromosome vector carrying a KSHV genome into murine endothelial cells derived from bone marrow generated a cell that would induce a Kaposi-sarcoma-like tumour when transplanted into mice. Sublines that had lost the KSHV genome in the absence of drug selection lost their tumour-inducing potential, as did KSHV-genome carrying cells, in which the expression of vGPCR had been silenced by siRNA (Mutlu *et al.*, 2007).

(b) Persistence of the KSHV genome

Similarly to the Epstein-Barr virus (EBV), KSHV is capable of replicating its latent episomal genome synchronously with the host cell cycle. However, latent genomes do not appear to persist efficiently in infected primary endothelial cells, nor in epithelial, endothelial or fibroblast cell lines (Foreman *et al.*, 1997; Renne *et al.*, 1998; Blackbourn *et al.*, 2000; Grundhoff & Ganem, 2004). In several cell lines, only a small subpopulation of cells are able to retain the virus in a stable manner following acute infection (Grundhoff & Ganem, 2004; An *et al.*, 2006).

(c) Chromosomal abnormalities, and alterations of specific proto-oncogenes

Most cases of Kaposi sarcoma are cytogenically normal. However, in some cases, the loss of Y-chromosomal sequences and the gain at 11q13 with an amplification of two oncogenes FGF4 and INT_2, as detected by comparative genome hybridization, have been noted (Kiuru-Kuhlefelt *et al.*, 2000; Pyakurel *et al.*, 2006). In short-term cultures of Kaposi sarcoma cells, numerical chromosomal abnormalities have been noted (Delli Bovi *et al.*, 1986; Scappaticci *et al.*, 1986; Saikevych *et al.*, 1988). Defined chromosomal abnormalities (loss of copies of chromosomes 14 and 21; deletions in the short arm of chromosome 3 at 3p14) were also noted in two permanent cell lines, KS-Y1 and KS-SLK, established from Kaposi sarcoma biopsies (Popescu *et al.*, 1996). Abnormalities at 3p14 were also noted in another permanent Kaposi sarcoma cell line, KS-IMM, in addition to further chromosomal changes (Casalone *et al.*, 2001).

No p53 mutations have been reported for the majority of Kaposi sarcoma. Host cell tumour-suppressor mRNAs are dysregulated in KSHV-associated-tumours.

4.3.2 Primary effusion lymphoma

(a) Requirement of KSHV expression for cell growth and invasion

In primary effusion lymphoma cell lines, siRNA- and shRNA-mediated knockdown of several latent genes, in particular vFLIP and vIRF-3, induces apoptotic death (Godfrey *et al.*, 2005; Guasparri *et al.*, 2006; Wies *et al.*, 2008). This suggests that these viral genes need to be continuously expressed to ensure the survival of primary effusion lymphoma cells.

(b) Persistence of the KHSV genome

B-Lymphoma cell lines derived from primary effusion lymphoma, contrary to most KSHV-infected cells, retain a stable latent viral genome in high copy numbers (50–100 copies/cell) (Cesarman *et al.*, 1995a, b; Boshoff *et al.*, 1998; Katano *et al.*, 1999; Morand *et al.*, 1999).

Knockdown of LANA in primary effusion lymphoma cell lines leads to a reduction in the viral genome copy numbers, this in keeping with the accepted role of LANA in episome replication (Godfrey *et al.*, 2005)

(c) Chromosomal abnormalities

In primary effusion lymphoma cells, complete or partial trisomy 12, trisomy 7, and abnormalities of bands Iq21–25 were noted frequently in addition to mutations in the 5′ untranslated region of the *BCL-6* gene (Gaidano *et al.*, 1999; Wilson *et al.*, 2002). Additional chromosomal changes were noted in the studies by Wilson *et al.* (2002) and by Nair *et al.* (2006).

No p53 mutations have been reported for the majority of primary effusion lymphoma.

4.3.3 Multicentric Castleman disease

Multicentric Castleman disease is a polyclonal lymphoproliferative disease that can be a precursor to frank lymphoma. In addition to LANA, vIL6 is expressed in multicentric Castleman disease B cells (see Section 4.2.4). Because vIL6 is a potent stimulator of B-cell growth, it is likely that this protein plays an important role in the B-cell proliferation seen in multicentric Castleman disease.

4.4 Interaction between KSHV and environmental agents

Many agents have an impact on the biology of KSHV:

1. EBV is present in 70–90% of primary effusion lymphomas. EBV-positive and EBV-negative primary effusion lymphomas can be distinguished from each other on the basis of host gene transcription (Fan *et al.*, 2005). However, no differences in clinical appearance, tumorigenicity in mice or response to therapy have been observed between EBV-positive and EBV-negative primary effusion lymphomas (Keller *et al.*, 2000; Petre *et al.*, 2007).
2. Cytomegalovirus (CMV) can reactivate KSHV, and the suppression of CMV has been shown to suppress KSHV viral loads (Martin *et al.*, 1999; Vieira *et al.*, 2001). However, at the time of writing, no evidence for a direct role for CMV in Kaposi sarcoma or primary effusion lymphoma exists.
3. HIV type 1 can reactivate KSHV and enhance KSHV infectivity (Mercader *et al.*, 2000; Merat *et al.*, 2002; Aoki & Tosato, 2004; Zeng *et al.*, 2007). These phenotypes are likely to be mediated by cell-derived cytokines. HIV tat protein can cause endothelial cell proliferation in experimental models (Ensoli *et al.*, 1990, 1994). However, Kaposi sarcoma and primary effusion lymphoma develop in the absence of HIV (Cesarman *et al.*, 1996). Even in HIV-infected patients, these two viruses have never been found in the same cells (Delli Bovi *et al.*, 1986).

To explain the well known high incidence of endemic KSHV in certain parts of Africa, it has been postulated that environmental agents might affect KSHV reactivation. In fact, natural, chemical and environmental products can reactivate KSHV from latency, most notably sodium butyrate and phorbol esters or plant extracts (Renne *et al.*, 1996; Zhong *et al.*, 1996; Miller *et al.*, 1997; Zoeteweij *et al.*, 1999; Whitby *et al.*, 2007).

4.5 Animal models

Following injection to experimental animals, KSHV can infect non-human primates (Renne *et al.*, 2004), NOD-SCID mice (Parsons *et al.*, 2006), and humanized SCID mice (Dittmer *et al.*, 1999; Foreman *et al.*, 2001; Wu *et al.*, 2006). These infections do not result in the formation of tumours. Nevertheless, they confirm the viral tropism (B cells and endothelial cells), and drug susceptibility (ganciclovir) *in vivo*. KSHV homologous viruses exist in the bank vole-mouse (MHV-68), and virtually in all non-human primates (Ensser & Fleckenstein, 2007). The infection of macaques with rhesus rhadinovirus in the context of Simian immunodeficiency virus (SIV) induces B-cell lymphoma and endothelial-cell hyperplasia (Mansfield *et al.*, 1999; Wong *et al.*, 1999).

Multiple tumourgraft models of Kaposi sarcoma and primary effusion lymphoma have been established (Boshoff *et al.*, 1998; Staudt *et al.*, 2004; Wu *et al.*, 2005; An *et al.*, 2006; Mutlu *et al.*, 2007; Sin *et al.*, 2007).

4.6 Transgenic mice models

An alternative approach to infection studies is to use transgenic mice where individual KSHV proteins are expressed in the hope of replicating selected aspects of KSHV pathogenesis. There are some limitations to single transgenic models. Whereas lymphoproliferative lesions and lymphomas in mice are easily classified on the basis of histology and marker–gene expression, this is not the case for endothelial cell tumours. They are referred to as Kaposi-sarcoma-like lesions, but can easily be mistaken for fibrosarcomas (Table 4.3).

4.6.1 Transgenic mice for KSHV latent genes

(a) LANA/ORF 73

The KSHV latent promoter (LANAp) showed B-cell lineage specificity in transgenic mice (Jeong *et al.*, 2002). KSHV LANA expression in transgenic mice resulted in 100% B-cell hyperplasias and lymphomas at about twice the rate of background in the C57/BL6 strain of mice (Fakhari *et al.*, 2006).

(b) vCYC/ORF 72

Whereas *vCYC* single transgenic mice did not develop tumours, lymphomas developed rapidly in a *p53*-null background (Verschuren *et al.*, 2002, 2004). [The Working Group noted that, presumably, loss of p53 counteracted the pro-apoptotic signals that are associated with forced vCYC expression.]

(c) vFLIP/ORF 71

The vFLIP transgenic mice exhibited an increased incidence of lymphoma (Chugh *et al.*, 2005).

4.6.2 Transgenic mice for KSHV lytic genes

(a) vGPCR/ORF 74.

vGPCR transgenic mice activated the same signalling pathways as predicted from human culture studies, and exhibited Kaposi-sarcoma-like lesions (Yang *et al.*, 2000; Holst *et al.*, 2001; Guo *et al.*, 2003; Montaner *et al.*, 2003; Jensen *et al.*, 2005; Grisotto *et al.*, 2006). Tumour formation required the chemokine binding as well as the constitutive signalling activities of vGPCR (Holst *et al.*, 2001). vGPCR was required for lesion initiation, though it was not essential once a fully malignant tumour had formed (Grisotto *et al.*, 2006).

(b) K1/VIP

K1 transgenic mice also exhibited Kaposi-sarcoma-like lesions and lymphomas (Prakash *et al.*, 2002, 2005).

Table 4.3 Transgenics for modelling KSHV-associated cancers

Viral Gene	Promoter	Incidence	Mean time to onset, days	Reference
Primary effusion lymphoma/multicentric Castleman disease				
MHV68vCYC1	Lck	40%	240	van Dyk *et al.* (1999)
vCYC	Eμ	17%	300	Verschuren *et al.* (2002)
vCYC/p53^{del}	Eμ	100%	80	Verschuren *et al.* (2004)
vFLIP	H2Kb	11%	600	Chugh *et al.* (2005)
LANA	LANAp	10%	300	Fakhari *et al.* (2006)
K1/VIP	SV40	15%	≥ 420	Prakash *et al.* (2002, 2005)
Kaposi sarcoma				
vCYC	VEGFR-3	80%	≥ 200	Sugaya *et al.* (2005)
K1	SV40	15%	≥ 420	Prakash *et al.* (2002, 2005)
vGPCR	hCD2-rtTA + TRE-vGPRC (Doxocyclin inducible transgenic system)	100%	≥ 150	Grisotto *et al.* (2006), Jensen *et al.* (2005)
vGPCR	SV40	30%	≥ 360	Guo *et al.* (2003)
vGPCR	hCD2	100%	90	Holst *et al.* (2001), Yang *et al.* (2000)

Modified from Damania & Dittmer (2008), and compiled by the Working Group

4.7 Synthesis

The available mechanistic data strongly support an oncogenic role of KSHV in human cancer.

KSHV alters the growth properties of endothelial cells in culture, and induces Kaposi-sarcoma-cell-like morphology (spindle cells).

One or several KSHV gene products are expressed in all KSHV-associated cancers in all KSHV-infected tumour cells.

At the molecular level, KSHV-encoded gene products associated with latent viral infection induce cell proliferation, block apoptosis, induce genomic instability or modulate cell migration and tumour progression.

Mechanistic data strongly support an oncogenic role of KSHV in primary effusion lymphoma and in Kaposi sarcoma in immunocompromised (post-transplant patients, AIDS patients), as well as in immunocompetent individuals.

KSHV proteins like vIL6 induce B-cell proliferation, and are expressed in KSHV-associated multicentric Castleman disease, strongly suggesting that infection with KSHV is causally associated with this lymphoproliferative disease.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of KSHV. KSHV causes Kaposi sarcoma and primary effusion lymphoma. Also, a positive association has been observed between exposure to KSHV and multicentric Castleman disease.

For multiple myeloma, there is *evidence suggesting lack of carcinogenicity.*

KSHV is *carcinogenic to humans (Group 1).*

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