Kaposi Sarcoma-Associated Herpesvirus

CAS No.: none assigned

Known to be a human carcinogen

Also known as KSHV or human herpesvirus 8 (HHV-8)

Carcinogenicity

Kaposi sarcoma-associated herpesvirus (KSHV) is *known to be a human carcinogen* based on sufficient evidence from studies in humans. This conclusion is based on evidence from epidemiological and molecular studies, which show that KSHV causes Kaposi sarcoma, primary effusion lymphoma, and a plasmablastic variant of multicentric Castleman disease, and on supporting mechanistic data. KSHV causes cancer, primarily but not exclusively in people with suppressed immune systems, by coding for protein and RNA products that work together to transform host cells into cancer cells and promote their survival and growth. These viral products are made (through the use of host-cell machinery) both when KSHV is in the lytic phase (destroying the infected cell during replication) and when it is latent (maintaining its DNA in the infected cell without destroying the cell) (Mesri *et al.* 2010, Fukumoto *et al.* 2011). KSHV virus is latent in most infected cells.

Cancer Studies in Humans

The majority of human cancer studies of KSHV have focused on Kaposi sarcoma (a cancer of the cells that line blood or lymph vessels). Kaposi sarcoma has four main subtypes: (1) epidemic, or related to human immunodeficiency virus type 1 (HIV-1) infection, (2) iatrogenic (resulting from medical treatment, such as organ transplants), (3) classic (a slow-growing form found mostly in older men in specific populations, such as in Mediterranean countries or among East Europeans of Jewish descent), and (4) endemic (found in sub-Saharan Africa, mostly among men but also among children).

Other cancer end points, including two rare B-cell non-Hodgkin lymphomas (primary effusion lymphoma and multicentric Castleman disease), also have been linked to KSHV. Primary effusion lymphoma (also called body-cavity-based B-cell lymphoma) arises in a specific type of immune cell (B lymphocytes) and comprises approximately 2% to 4% of HIV-1-related non-Hodgkin lymphomas (Simonelli *et al.* 2003, Sullivan *et al.* 2008). Multicentric Castleman disease also arises in B lymphocytes; it has several histological variants (hyaline vascular, plasma cell, mixed, and plasmablastic), and KSHV is associated with the plasmablastic variant.

Kaposi Sarcoma

Evidence for an association between KSHV infection and Kaposi sarcoma is based on consistent findings of increased risk in epidemiological studies with different designs and in different populations and on the presence of an exposure-response relationship between the degree of viral infection and the cancer.

Over 90% of Kaposi sarcoma patients are infected with KSHV, and KSHV DNA is found in virtually all Kaposi sarcoma tumors; KSHV is therefore considered to be a prerequisite for diagnosis of this cancer (Chang *et al.* 1994, Mesri *et al.* 2010, Cavallin *et al.* 2014). The association between KSHV and Kaposi sarcoma has been evaluated in about 80 case-control studies and 25 cohort studies or studies of cases and controls identified within the cohorts (IARC 2012, NTP 2016). In the case-control studies, patients with all four types of Kaposi sarcoma were often 10 times and sometimes over 100 times more likely to be infected with KSHV than were individuals without Kaposi sarcoma. In the cohort studies, KSHV-infected individ-

uals were 2 to 16 times more likely to develop Kaposi sarcoma than were uninfected individuals. In some studies, the risk of Kaposi sarcoma increased with increasing viral load of KSHV (Sitas *et al.* 1999, Newton *et al.* 2003a,b, 2006, Albrecht *et al.* 2004).

Most KSHV-infected patients who develop Kaposi sarcoma have immune systems compromised either by HIV-1 infection or as a result of drug treatments after organ or tissue transplants. The timing of infection with HIV-1 may also play a role in development of Kaposi sarcoma. Acquiring HIV-1 infection prior to KSHV infection may increase the risk of epidemic Kaposi sarcoma by 50% to 100%, compared with acquiring HIV-1 infection at the same time as or after KSHV infection. Nevertheless, patients with the classic or endemic forms of Kaposi sarcoma are not suspected of having suppressed immune systems, suggesting that immunosuppression is not required for development of Kaposi sarcoma.

Primary Effusion Lymphoma

Evidence for an association between KSHV infection and primary effusion lymphoma is based on consistent findings from over 115 KSHV-infected patients reported in a large number of case reports, several small case series, and a case-comparison study (IARC 2012, NTP 2016), together with histological confirmation of the tumors' specific morphological and immunological features. These cases of primary effusion lymphoma were identified in different populations, including both HIV-1-positive and HIV-1-negative patients, organ-transplant recipients, and people from areas where the risk of endemic or classic Kaposi sarcoma is known to be high (Dotti *et al.* 1999, Boulanger *et al.* 2008, Testa *et al.* 2010, IARC 2012). In addition, some patients with primary effusion lymphoma also had other KSHV-associated cancers, including Kaposi sarcoma and multicentric Castleman disease. The strong association of KSHV with primary effusion lymphoma led to the adoption of the presence of KSHV infection as a diagnostic criterion for this specific pathologic entity. Primary effusion lymphoma in HIV-1-positive patients exhibits rapid progression with short survival times, whereas progression in HIV-1-negative patients and patients with normal immune responses appears to be much slower (IARC 1997), suggesting that immunosuppression is an important cofactor in KSHV carcinogenicity.

Studies of tumor tissue provide evidence for a causal role of KSHV in primary effusion lymphoma. These studies have shown that primary effusion lymphoma cells contain high levels (50 to 100 copies) of KSHV DNA and have patterns of viral gene products (RNA or protein) very similar to those observed in Kaposi sarcoma. Importantly, primary effusion lymphoma lesions arise from a single KSHV-infected B cell (i.e., are monoclonal), suggesting that KSHV infection precedes tumor growth (Katano *et al.* 1999, Judde *et al.* 2000, Fukumoto *et al.* 2011, IARC 2012, Giffin and Damania 2014).

Multicentric Castleman Disease

Two types of evidence establish a link between KSHV infection and the plasmablastic variant of multicentric Castleman disease. The first consists of nine case-series studies and four case-comparison studies, which provide, although not conclusively, evidence for an association between KSHV infection and all types of multicentric Castleman disease, and the second consists of molecular analysis of this type of the tumor tissue, which demonstrates that the association between KSHV infection and multicentric Castleman disease is strongest for the plasmablastic variant of this disease (NTP 2016). (The plasmablastic variant arises in plasmablasts, which are immature precursors of antibody-producing B lymphocytes.)

KSHV has been detected in about half of all multicentric Castleman disease cases (all variants) reported in the literature, but has

only rarely been detected in patients without cancer (i.e., in only 1 of almost 200 controls in the case-comparison studies). It is more common among multicentric Castleman disease patients who are also infected with HIV-1 than in HIV-1-negative patients, suggesting that immunosuppression is important for cancer development (Parravicini *et al.* 1997a, Oksenhendler *et al.* 2002, 2013). Moreover, the level of KSHV DNA in circulating white blood cells or blood plasma is related to the occurrence of symptoms during multicentric Castleman disease flares in HIV-1-positive individuals (Reddy and Mitsuyasu 2011).

Studies characterizing the tumor tissue have shown that plasmablasts in KSHV-associated multicentric Castleman disease have a unique molecular profile and produce a distinctive monotypic form of immunoglobulin M; these plasmablasts are not found in KSHV-negative multicentric Castleman disease (Dupin *et al.* 2000). Therefore, KSHV-associated (plasmablastic) multicentric Castleman disease is now recognized as an entity distinct from other forms of multicentric Castleman disease; it is classified by the World Health Organization as "a large B-cell lymphoma arising in HHV8- [KSHV-] associated multicentric Castleman disease" (IARC 2008). In KSHV-associated multicentric Castleman disease cells, it appears that KSHV proteins are produced both when the virus is latent and when it is replicating. These proteins include a virally encoded interleukin 6, which stimulates proliferation of mature B lymphocytes and causes inflammation, and thus may play a role in carcinogenicity (Aoki *et al.* 2001, Burbelo *et al.* 2010, Fukumoto *et al.* 2011, Giffin and Damania 2014).

Studies on Mechanisms of Carcinogenesis

KSHV-associated cancer develops through a complex process that involves interactions among many viral, host, and environmental factors (Fukumoto *et al.* 2011, Mesri *et al.* 2014). Both *in vitro* and animal models have been developed that accurately reproduce many features observed in KSHV-associated cancer (An *et al.* 2006, Mutlu *et al.* 2007, Mesri and Cesarman 2011, Ashlock *et al.* 2014, Dittmer *et al.* 2015); however, not all aspects of viral infection and transformation into cancer cells are well understood (Fukumoto *et al.* 2011, Giffin and Damania 2014).

In an immune-compromised individual, KSHV-infected cells escape recognition and destruction by the immune system and are able to produce cancer-causing viral RNA or proteins (Cavallin *et al.* 2014, Mesri *et al.* 2014). Viral products made during the lytic phase mimic or disrupt host cytokine signals (communication among cells), creating conditions that promote tumor growth, proliferation of latently infected cells, development of blood vessels, inflammation, and evasion or alteration of the immune response and antiviral response (Mesri *et al.* 2010, Wen and Damania 2010, Fukumoto *et al.* 2011, Cavallin *et al.* 2014). In addition, some latently infected cells are less likely to provoke an immune response and may progressively transform into cancer cells through inhibition of programmed cell death (apoptosis) and maintenance of viral latency (see NTP 2016).

Biological Properties

KSHV is an enveloped double-stranded DNA gamma-2 herpesvirus (rhadinovirus) that was first identified in humans in 1994 in association with acquired immunodeficiency syndrome (AIDS) (Chang *et al.* 1994, IARC 1997, Fukumoto *et al.* 2011). A lipid membrane envelope surrounds a layer of viral proteins, which encloses a viral capsid (protein shell) and a linear 165-kb genome (IARC 1997, 2012, Fukumoto *et al.* 2011, Giffin and Damania 2014). KSHV infects many types of cells, including both immune cells (B lymphocytes, dendritic cells, and monocytes) and non-immune cells (keratinocytes, fibroblasts, and prostate cells) (IARC 1997, 2012, Fukumoto *et al.* 2011, Campbell

et al. 2014, Giffin and Damania 2014). Certain immune cells (CD19^{+} B lymphocytes) are a long-term reservoir for the latent virus. KSHV glycoproteins bind to several host-cell receptors and initiate viral entry by an inward folding of the host cell membrane to form a small capsule within the cell that contains the virus attached to its receptor (Giffin and Damania 2014). The virus can reproduce through the lytic cycle, which destroys the infected cell, or can remain latent as a viral episome, consisting of circular DNA separate from the infected cell's chromosomes, which can use the cell's machinery to replicate along with the infected cell's own DNA.

Detection

KSHV is detected most commonly by measurement of anti-KSHV antibodies, and also by detection of DNA and viral proteins in tissues (Parravicini *et al.* 1997b, 2000, Fukumoto *et al.* 2011, Bhutani *et al.* 2015, Xu *et al.* 2015). Tests are available for detecting antibodies to proteins produced in the latent and lytic phases. These tests vary in sensitivity and specificity, but have generally improved over time. Different viral proteins are made during different phases of the viral life cycle (latent or lytic), and an individual's antibody response to these proteins varies, which makes it difficult to compare the prevalence of KSHV in different populations (IARC 1997, 2012, Fukumoto *et al.* 2011). Viral DNA can be detected in tumor tissue by polymerase chain reaction (IARC 1997, Fukumoto *et al.* 2011, Campbell *et al.* 2014).

Exposure

Prevalence studies measuring antibodies to KSHV in serum have shown that a significant number of people in the United States are infected with KSHV. In the first systematic evaluation of KSHV epidemiology in the U.S. general population (based on tests for KSHV antibodies in serum samples from the Third National Health and Nutrition Examination Survey, 1988–1994), overall prevalence of KSHV antibodies was approximately 7% and was similar in men and women (Engels *et al.* 2007). A previous study of 1,000 U.S. blood donors (sampled in 1994 and 1995) reported estimated prevalence of KSHV antibodies ranging from 0.5% to 5% (Pellett *et al.* 2003, IARC 2012). KSHV prevalence rates appear to vary widely among different populations, from 2% to 3% in northern Europe to over 50% in some sub-Saharan African populations (IARC 2012). However, even outside of areas where KSHV is endemic, prevalence rates among men having sex with men have been reported in the range of 30% to 60% for HIV-1-positive men and 20% to 30% for HIV-1-negative men (Martin *et al.* 1998, O'Brien *et al.* 1999, Phillips *et al.* 2008).

Transmission

KSHV is thought to be transmitted primarily via saliva (IARC 2012). The presence of KSHV in peripheral blood suggests that it can also be spread via blood, and transmission has been reported in injection drug users, in transfusion recipients, and from organ-transplant donors to recipients (Barozzi *et al.* 2003, IARC 2012). In populations in which KSHV infection is endemic, it can be transmitted from mother to child, especially among children between the ages of 6 and 10 years, and infection rates increase with age. Risk factors for infection may include contact with infected family members, contact with contaminated water, and, in particular, HIV-1 infection (IARC 2012). There is also some evidence for spouse-to-spouse transmission among heterosexual couples, which appears to be more efficient from female to male than male to female (Dupuy *et al.* 2009).

Factors that increase the risk of HIV-1 infection (e.g., number of sexual partners) also increase the risk of infection with KSHV (Smith *et al.* 1999, Engels *et al.* 2007, IARC 2012), and orogenital sex has been shown to be significantly correlated with development of KSHV an-

tibodies in men who have sex with men (Dukers *et al.* 2000). It is unclear whether KSHV is sexually transmitted in heterosexuals. It has also been suggested that application of virus-carrying saliva to the sites of insect bites (to relieve itching) could facilitate the transmission of KSHV (Coluzzi *et al.* 2003, Amodio *et al.* 2011).

Diseases (Non-Cancer), Prevention, and Treatment

Most otherwise healthy individuals who are infected with KSHV show no symptoms (DHHS 2013a, ACS 2014, NCI 2014). There are very few reports of primary infection with KSHV. Symptoms associated with initial KSHV infection include fever, a measles-like skin rash, diarrhea, fatigue, swollen lymph nodes, enlarged spleen, blood-cell deficiencies, and bone-marrow failure with an excess of B lymphocytes (Luppi *et al.* 2000a, Wang *et al.* 2001, Andreoni *et al.* 2002). Active KSHV infection may be associated with fever, skin rash, and hepatitis (Luppi *et al.* 2000b). There is conflicting evidence regarding suggested associations of KSHV infection with actinic keratosis or with the autoimmune skin diseases pemphigus vulgaris and pemphigus foliaceus (Ablashi *et al.* 2002). KSHV has been found in inflammatory cells in isolated cases of interstitial pneumonitis (an autoimmune-related lung disease), in sarcoid tissue (lesions formed in sarcoidosis, an inflammatory disease), and in histocytic necrotizing lymphadenitis (a lymph-node disorder), but a causal role for KSHV in these diseases has not been established.

Because KSHV transmission is associated with KSHV shedding in saliva and occasional shedding in genital secretions, avoiding salivary exposure (e.g., via kissing or sharing food, drink, or toothbrushes) and following safe sexual practices may theoretically prevent transmission (Chang-Moore Laboratory 2009, DHHS 2013a,b). Some drugs have been reported to reduce or inhibit KSHV shedding; however, no FDA-approved drugs currently exist for treatment of KSHV infection. Highly active antiretroviral therapy was associated with an 89% decrease in KSHV shedding frequency (Cattamanchi *et al.* 2011). There is no vaccine against KSHV, but limited vaccine development efforts are ongoing (Wu *et al.* 2012, ACS 2014).

Regulations

Department of Transportation (DOT)

Infectious substances are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Guidelines

American Society of Transplantation (AST)

The AST has issued guidance for the diagnosis, prevention, and treatment of KSHV infection after solid (vascular) organ transplantation. AST guidelines do not specifically prohibit solid organ transplantation because of KSHV seropositivity in either the donor or the recipient. They do advise that serologic screening be considered for donors and recipients from geographic regions with high rates of KSHV infection.

Food and Drug Administration (FDA, an HHS agency)

The FDA has issued numerous guidance documents prescribing procedures (e.g., use of standardized labels, abbreviated donor screening questionnaires) for reducing the risk of virus transmission by blood and blood products.

Health Resources and Services Administration (HRSA, an HHS agency)

KSHV infection is included as part of a list of potential donor-derived disease transmission events (PDDTE) reported through 2010 in the Organ Procurement and Transplantation Network's (OPTN) guidance for reporting PDDTE; however, these guidelines do not specifically prohibit solid organ transplantation because of KSHV seropositivity in the donor.

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