KSHV

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Kaposi's sarcoma-associated herpesvirus (KSHV), or human herpesvirus-8 (HHV-8), is an oncogenic γ-herpesvirus which is the etiological agent of the most prevalent AIDS-related malignancy, Kaposi's sarcoma (KS). KSHV is also the causative agent of two lymphoproliferative disorders, the rare Multicentric Castleman disease (MCD) and primary effusion lymphoma (PEL). KSHV inflammatory cytokine syndrome (KICS) can also be attributed to KSHV infection.

Kaposi's Sarcoma Herpes Virus (KSHV) | Kaposi's sarcoma | Multicentric castelman disease | Primary effusion lymphoma | KSHV inflammatory cytokine syndrome

1. Epidemiology

KSHV prevalence varies geographically with the highest prevalence in general adult populations in Sub-Saharan Africa (SSA, seroprevalence 30–50%) and the Mediterranean region (20–30%) and low prevalence in Western and Northern Europe, Asia and North and South America (5–10%)[1][2][3]. Higher prevalence has been noted in people who have certain behavioural risk factors, such as men who have sex with men (20–40%) in the United States of America (USA) and Northern Europe[4][5], or people of specific ethnicities regardless of HIV infection, such as Uganda (14–86%) and the Ivory Coast (43–100%) where there is risk for endemic KS, and the Mediterranean region (20–30%), at risk for classic KS[3][6]. In HIV-infected people in the USA on ART, prevalence was 38%[7].

2. Classification and structure

Based on variability in the KSHV K1 gene sequence, KSHV has been classified into 7 major subtypes: A, B, C, D, E, F and Z[8]. The different subtypes have been shown to have variable penetrance in various population groups and are distributed along broad geographic and ethnic lines, and it has been proposed that different genotypes may have different pathogenic and tumorigenic properties[9]. Subtypes B and A5 have been suggested to predominate in SSA[8][10][11] while subtypes F and E are found particularly in Uganda and Brazil, respectively. Subtypes A, C and D are found more broadly in the Americas and Northern Europe, the USA and Eurasia and Asia, respectively[9][12][13].

KSHV is a γ2 herpesvirus of the genus *Rhadinovirus*[14]. KSHV virions, with an average diameter of 100 nm, consist of a double-stranded DNA genome encased in a capsid, a tegument and a glycoprotein containing lipid envelope, resembling the structure of other herpesviruses like Epstein-Barr Virus[15][16][17]. The KSHV envelope contains glycoproteins that play essential roles in KSHV entry (see section 3)[18][19][20][21]. The approximately 140

kb DNA genome encodes 87 open reading frames (ORF), the majority of which are common to herpesviruses while 20 so-called ‘K genes’ are unique. KSHV encodes at least 14 cellular orthologues pirated from human genes, characteristic of rhadinoviruses, and 17 viral microRNAs (miRNAs)[3][19]. The KSHV episome contains a latency-associated region encoding transcripts that characterise the KSHV latent cycles, while lytic transcripts are encoded on the remainder of the episome[3]. A number of latency-associated genes are oncogenes, such as latency-associated nuclear antigen (LANA), viral-encoded Cyclin (vCyclin) and viral FADD-like interleukin-1-converting enzyme (FLICE) inhibitory protein (vFLIP)[3].

3. Viral transmission and entry

Saliva is thought to be the primary route of transmission, however KSHV has also been detected in breast milk, semen and blood[22][23]. As is typical for herpesviruses, KSHV has a very broad host cell tropism in vitro and in vivo. In vivo, KSHV can infect endothelial cells, B cells, epithelial cells and fibroblasts, to name a few significant examples[24]. Herpesviruses typically engage multiple cell surface receptors with their envelope glycoproteins to gain access. Some of these host molecules are required for binding to concentrate the virus on the cell surface, while others facilitate entry[25]. The process of KSHV entry into target cells is complex and engages several viral glycoproteins (see section 3.1) which bind to a large range of host cell surface molecules[39]. Receptors for KSHV include heparan sulphate proteoglycans (HSPGs), several integrins and Eph receptors, cystine/glutamate antiporter (xCT) and Dendritic Cell-Specific Intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN). This diverse range of potential binding and entry sites allows KSHV to have a broad cell tropism, and entry into specific cells is dependent on the available receptor repertoire.

Following binding and making use of cellular signaling molecules, KSHV enters cells utilizing diverse endocytic pathways including clathrin- and caveolin-mediated endocytosis, macropinocytosis and undefined endocytic entry pathways, depending on the cellular context[26]. Thereafter, the viral envelope fuses with the membrane of the endosome, likely triggered by low pH as in other herpesviruses, and the capsid is released into the perinuclear region. The KSHV genome enters the nucleus via nuclear pores where the linear genome rapidly undergoes circularization into an episome[27][17][28][29].

3.1 KSHV Envelope Glycoproteins

Preliminary attachment to the host cell surface and the subsequent entry of KSHV is mediated by glycoproteins embedded in the virus envelope. The virion envelope contains several conserved herpesvirus glycoproteins, namely gB, gH, gL, gM and gN, which are encoded by the Open Reading Frames (ORFs) 8, 22, 47, 39, and 53, respectively[19][30][31]. The glycoproteins gpK8.1A and B, ORF4, ORF27, ORF28 and ORF68, associated with the lytic cycle, and ORF45, an RSK activator protein, are unique to KSHV[19][31][32][33][34][35][36][37][38]. The glycoproteins considered essential to KSHV entry are K8.1, gB and the gH-gL heterodimer, and their engagement with specific cellular receptors is comprehensively reviewed here[39]. The particular repertoire of cellular receptors available to engage with specific glycoproteins eventually leads to a concerted series of molecular events culminating in fusion of the viral envelope with the host cell membrane. It is widely accepted that gB, which is comprised of five

functional domains typical for type III fusion glycoproteins, is the initial cell binding protein[40] and key fusogen leading to virus entry and infection, and that low pH may facilitate gB-mediated KSHV fusion[29]. A study of individuals from diverse geographical locations infected with KSHV showed that gB was highly conserved[11] and that KSHV infectivity could be neutralised by rabbit anti-gB antibodies[40]. Besides gB, the gH-gL heterodimer is required for fusion[41], and is hypothesized to play an important role specifically in the post-binding steps of KSHV infection, as treatment with anti-gH and anti-gL antibodies inhibited KSHV infection of target cells without blocking binding of the virus to the cell surface[30]. Recently, gH-gL has also been found to bind to KSHV entry receptors on host cells[42].

The KSHV K8.1 gene is alternatively spliced to form two separate glycoproteins, K8.1A and K8.1B, with the A protein being dominant on the viral envelope[32][20][43]. Like gB, K8.1A also facilitates attachment to target cells by binding to heparan[20], but it is not necessary for infection[21].

4. KSHV-associated diseases

Primary KSHV infection, while often silent, may sometimes be associated with nonspecific symptoms including fatigue, rash, diarrhoea and lymphadenopathy[44]. In immunocompetent individuals, the lifelong course of KSHV infection is clinically silent even during intermittent lytic activation, likely controlled by T-cell responses[45][44][46]. However, with a decline in T-cell immunity, most markedly due to HIV immunosuppression, KSHV-infected patients become more likely to develop KSHV-associated diseases[47].

KS was first described by a Hungarian dermatologist, Moritz Kaposi, in 1872 in a case description of six elderly men with angioproliferative tumours[48]. Over a century later, prompted by the peculiar geographic distribution of KS and the massive explosion of KS prevalence during the early AIDS epidemic, KSHV was discovered as the etiological agent of Classic, Endemic, Iatrogenic and AIDS-related KS[49]. Soon after, two additional diseases caused by KSHV were identified: PEL, a body-cavity-based B-cell lymphoma[50]; and a KSHV-associated plasmablastic form of MCD (KSHV-MCD)[51]. Recently, an IL-6 related inflammatory syndrome without an MCD diagnosis termed KICS was described[52]. These KSHV-associated diseases often present simultaneously in patients co-infected with KSHV and HIV which has implications for diagnosis and treatment strategies[53][54]. While all of these KSHV-associated diseases have been reported in other immunosuppressed and elderly people[55][56][57], HIV-related immune suppression (i.e. CD4 count <200 cells/μl) is one of the most important mechanisms that favours KSHV-driven pathogenesis[47].

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