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Pathogenesis and Associated Diseases of Kaposi's Sarcoma-associated Herpesvirus*

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Abstract: Kaposi's sarcoma-associated herpesvirus (KSHV) is the primary etiological agent of Kaposi's sarcoma, primary effusion lymphoma and muticentric Castleman's disease. In common with the other herpesviruses, KSHV exhibits both latent and lytic life cycles, both of which are characterized by distinct gene expression profiles and programs. KSHV encodes proteins which play essential roles in the inhibition of host adaptive and innate immunity, the inhibition of apoptosis, and the regulation of the cell cycle. KSHV also encodes several proteins which have transforming and intrcellular signalling activity.

Key words: Kaposi's sarcoma-associated herpesvirus (KSHV); Kaposi's sarcoma; Multicentric Castleman's disease

In 1872, the Hungarian dermatologist Moritz Kaposi reported five cases of skin idiopathic multiple pigmented sarcomas which were subsequently designated as Kaposi's sarcoma (KS) in 1891. In the 1970s, people started to take an infectious agent into account for the etiologic factor of KS disease. In 1994, Chang *et al* identified the presence of DNA fragments of a novel herpesvirus in tumor tissue specimens from a patient with acquired immunodeficiency syndrome (AIDS)-associated Kaposi's sarcoma (10), which initiated the unveiling of a new human herpesvirus designated as Kaposi's sarcoma-associated herpesvirus (KSHV) (also named as human herpesvirus 8). Since then, the causal link between KSHV and KS has been well established. KSHV has also been observed to be associated with a rare disease called primary effusion B cell lymphoma (7) and with an unusual B cell lymphoproliferative condition named multi-centric Castleman's disease, particularly in those arising in HIV-infected individuals (36).

KSHV-ASSOCIATED DISEASES

Kaposi's Sarcoma

Four clinical epidemiological variants of KS have been recognized: classic, endemic (Africa), transplantation associated (iatrogenic) and epidemic (AIDS associated). The lesions of KS have distinctive morphologic and histological features. Multifocal and usually painless skin involvement is typical, with the gradual appearance of reddish purple macules or

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patches of purple nodules on the legs (41). The histologic features are uniform, showing spindle-shaped tumor cells with extravasated red blood cells and hemosiderin in slits between irregular vascular spaces (41).

Primary effusion lymphoma

In 1989, a new peculiar lymphoma was described in HIV-positive patients (24). This lymphoma was firstly named as body cavity-based lymphoma, then renamed as primary effusion lymphoma (PEL). KSHV/HHV-8 is invariably present in PEL which is characterized as a monoclonal, non-Hodgkin's B cell lymphoma that frequently lacks B cell-specific surface markers (3, 8). PEL displays immunoblastic/centroblastic morphology and postgerminal center immunophenotype and is usually present without an apparent tumor mass but with effusion in the peritoneal, pleural or pericardial space (15).

Multicentric Castleman's disease

Castleman's disease (angiofollicular lymphoid hyperplasia or giant lymph node hyperplasia) is a rare, nonmalignant, usually polyclonal form of lymphadenopathy. Three histologic types have been identified: hyaline-vascular, plasma cell, and intermediate. Multicentric Castleman's disease (MCD) has an aggressive, often fatal clinical course and usually presents with multifocal lymphadenopathy and a variety of systemic symptoms, such as fever, rash, cytopenia, and hypergammaglobulinemia. MCD in AIDS patients is often associated with Kaposi's sarcoma and usually belongs to the plasma cell variant. KSHV DNA sequences were found in all HIV-related cases of MCD compared to less than half in HIV-negative cases (36). KSHV viral load in the peripheral blood of MCD patients seems to correlate with the severity of symptoms, worse prognosis, and exacerbation. In addition, patients with MCD may develop other KSHV-associated diseases, such as PEL, KS, or both.

PATHOGENESIS OF KSHV

KSHV is a large double-stranded DNA virus that replicates in the nucleus as a closed circular episome during latency but linearizes during virion packaging and replication. All KSHV transcripts that have been identified so far are encoded on a continuous 140.5 kb long unique region. The long unique region is flanked by the 20-35 kb terminal repeat region composed of 801-bp high G+C content (84.5%) terminal repeat units (32). Approximately 90 open reading frames (ORF) have been identified, and over 60 show homology with other rhadinoviruses. These ORFs are named and numbered following the nomenclature initially adopted for HVS. The genome also contains a number of genes unique to HHV-8, named K1 to K15.

KSHV contains genes that play roles in the inhibition of host adaptive and innate immunity, control of tumor suppressor pathways, and regulation of the cell cycle. Some proteins encoded by KSHV have transforming and intracellular signaling activity.

Interference with the adaptive immune system

Two transmembrane proteins, termed modulator of immune recognition (MIR) 1 and 2, are encoded by ORF K3 and ORF K5, respectively. They both efficiently inhibit MHC I surface expression. They remove MHC I from the plasma membrane through enhanced endocytosis and by targeting them for degradation by the proteasome (12). Both MIR proteins selectively reduce MHC class I but not class II. However, they display different specificities in downregulation of HLA allotypes. MIR2 significantly

downregulates HLA-A and -B and downregulates HLA-C only weakly, but not HLA-E, whereas MIR1 downregulates all four HLA allotypes (21). MIR1 and MIR2 may function by related but different mechanisms. MIR2 is an E3-ubiquitin ligase that initiates the ubiquitination of lysines in the C termini of its cellular targets (28). MIR1 is also an E3-ubiquitin ligase which promotes the down-regulation of MHC I molecules lacking lysine residues in their intracytoplasmic domain. MIR1 dominantly targets MHC class I complexes to dense lysosomal components via the trans-Golgi network (27).

KSHV encodes three secreted chemokines. These small 10 Kda proteins, including macrophage inflamematory proteins vMIP-1, vMIP-II and vMIP-III, are encoded by ORF K4, ORF K4.1 and ORF K6, respectively. Three KSHV chemokines are agonists for their corresponding receptors and belong to the CC chemokine family. VMIP-I is a CC receptor 8 (CCR8) agonist, vMIP-II binds and activates CCR3 (3) and vMIP-III is an agonist for CCR4 (38). CCR3, CCR4 and CCR8 are chemoattractant recptors on Th2 lymphocytes. KSHV inhibits effective Th1-like cell-mediated immune responses through secreting virus-encoded chemoattractant cytokines and recruiting Th2 cells to the site of infection (38), which may represent a novel mechanism to facilitate the polarization of Th2 immune responses. In addition to inhibiting Th1 immunity, all three viral chemokines induce a strong angiogenic response (3,38).

Innate immune evasion strategies

The KSHV ORF4 encodes a protein designated KSHV complement control protein (KCP), which has sequence homologies to human complement regulators (32). Three different KCP isoforms could be detected in KSHV-infected PEL cell cultures. All three isoforms regulate complement activation by inhibiting C3 deposition on the cell surface (37). HVS and MHV-68 have developed similar strategies to circumvent the component of the host immune response which plays an important role in limiting virus infection.

ORF K1 encodes a small transmembrane immunoglobulin like glycoprotein called VIP (variable, ITAM containing protein), which possesses a cytoplasmic Immunorecptor tyrosine activation motif (ITAM) similar to that of the BCR (17). It is shown that VIP can induce the expression and secretion of vascular endothelial growth factor (VEGF) in epithelial and endothelial cells. It is also shown that K1 induces expression of matrix metalloproteinase-9 (MMP-9) in endothelial cells (43). Therefore, VIP signaling may contribute to KSHV-associated pathogenesis through a paracrine mechanism by promoting the secretion of VEGF and MMP-9 into the surrounding matrix.

IFN activation is one of the first immune responses to virus infection. The KSHV open reading frame K9 encodes the Viral interferon (IFN) factor 1 (vIRF1), which downregulates IFN and IRF mediated transcriptional activation, and leads to cellular transformation in rodent fibroblasts and induction of tumors in nude mice. vIRF-1 can interact with GRIM19 (retinoid-IFN-induced mortality 19) both *in vivo* and *in vitro*, thus modulating IFN/RA-cell death signals (34). It also directly inhibits IFN-induced transcription by interacting with cellular IRF3, thereby preventing IRF3 recruiting P300 and CBP (CREB-binding protein) histone acetytransferase coactivators into the IFN transcriptional complex (25). vIRF1 can inhibit transforming growth factor-beta (TGF-beta)

signaling via its interaction with Smad3 and Smad4 (35). It has been shown that this interaction inhibits Smad3/Smad4 complexes from binding to DNA, and thus suppresses TGF-beta-mediated transcription and growth arrest (35).

KSHV encodes a human IL6 (hIL6) homologue (vIL-6, encoded by ORF K2). vIL6 is expressed regularly in the plasmablasts of MCD, in a minority of PEL cells and rarely in KS lesions. hIL6 and vIL6 differ in their receptor engagement and utilization. hIL6 binds first to gp80 and then forms a complex with the gp130 to stimulate cell growth, while vIL6 only requires gp130, one of the two cell surface IL6 receptor subunits. vIL-6, but not hIL6, protects PELs and multiple cells from the antiviral, cytostatic effects of IFN-α, which down-regulates the surface expression of gp80 but not gp130 (11). Thus vIL6 can bypass the regulatory checkpoint using different receptor interactions, and this may enable KSHV/HHV8 infected cells to escape the regulatory control of IL-6 signaling by interferon-α and overcome cell cycle arrest or apoptosis.

Inhibition of apoptosis

vBcl-2, a viral homologue of human Bcl-2, is encoded by KSHV ORF16. It possesses Bcl-2 homologue BH1 and BH2, but not the BH3 domains. vBcl-2 can inhibit bax-mediated apoptosis (33). The mechanism by which vBcL-2 inhibits apoptosis may be attributed to its interaction with the proapoptotic cellular protein Diva, which binds to the caspase-9 regulator Apaf-1 to prevent BCL-XL from blocking cell death (20).

Latency-associated nuclear antigen 1 (LANA1) is encoded by ORF73. LANA1 is present in nearly all infected cells from tumors and cell cultures and has a number of functions in the transcription and replication of viral episomal DNA, and tethers the circular viral DNA to the host chromatin during interphase and mitosis (1). LANA1 can bind to p53, a transcriptional regulator of cell cycle arrest and apoptosis, and efficiently prevents apoptosis induced by p53 overexpression (13).

KSHV encodes a viral FLICE-inhibitory protein (vFLIP) by ORF K13 , which bears a structural resemblance to the prodomain of caspase-8 and has been shown to protect cells against death-receptor-induced apoptosis *in vitro* and *in viv*o (2). KSHV vFLIP also possesses the unique ability of transforming Rat-1 and Balb/3T3 fibroblast cells, which is not shared by other vFLIPs (39). Elimination of vFLIP production in PEL cells by RNA interference results in significantly decreased NF-kappaB activity, down-regulation of essential NF-kappaB-regulated cellular prosurvival factors, induction of apoptosis, and enhanced sensitivity to external apoptotic stimuli (18).

Regulation of the cell cycle

A third cellular function targeted by KSHV regulatory proteins is control of the cell cycle. v-cyc is a homologue of cellular D and E-cyclins. v-cyc can interact with CDK6 and to a lesser extent with CDK4 and CDK5. These interactions will phosphorylate pRB and thereby inactivate pRB. Phosphorylation of pRB will overcome G1 arrest and progress cells through the cell cycle (40). v-cyclin is expressed in the majority of the malignant cells that are associated with KSHV infection in humans, which renders v-cyclin a putative viral oncogene.

LANA-1 also binds to pRB in the pocket region and acts as a transcription cofactor protein to activate the transcription of genes involved in the cell cycle

(42). LANA1 can interact with GSK-3ß, a kinase involved in phosphorylation and subsequent degradation of ß-catenin by the proteasome, thus inhibiting ß-catenin degradation and increasing ß-catenin levels, thereby leading to the activation of promoters containing Lef/Tef-binding sites and subsequent to entry into S-phase (14).

K-bZIP, the protein encoded by the open reading frame K8 of KSHV, is a member of the basic region-leucine zipper family of transcription factors. K-bZIP inhibits cell cycle progression by inducing $p21^{CIP}$ through CCAAT/enhancer-binding protein OE/EBPα (44). This may activate the G2/M checkpoint and prevent mitosis to maximize viral DNA synthesis.

Proteins with transforming and intracellular signaling activity

KSHV-GPCR is a G-protein coupled receptor and a homolog of the human interleukin 8 (IL-8) receptor (9). KSHV-GPCR signals via multiple transduction pathways including activation of nuclear factor-kappa B, activating PI3-kinase, p42/44 MAPK and AKT/pKB, and activating JNK/SAPK, p38 MAPK and RAFTK. It has been reported that expression of KSHV-GPCR resulted in the development of angioproliferative KS like tumors in transgenic mice (45). KSHV-GPCR modulates the transcription of angiogenesis-regulatory genes, proinflammatory genes and cytokines (29, 31).

A group of transcripts originating in the K12/Kaposin locus has been reported to encode several proteins. It has been shown that kaposin A induces lymphocyte aggregation and adhesion through direct interaction with cytohesin-1, a guanine nucleotide exchange factor for GTPase and regulator of integrin-mediated cell adhesion (23). Kaposin B can increase the expression of cytokines by blocking the degradeation of their messenger RNAs (mRNAs), by binding to and activating the kinase MK2, a target of the p38 mitogen-activated protein kinase signaling pathway and a known inhibitor of ARE-mRNA decay (26).

The products of three immediate-early or early genes ORF K1/VIP, ORF K9/VIRF-1, ORF74/vGPCR have been shown to have transforming properties and can induce cellular signaling pathways. VIP and vGPCR cause tumors in transgenic mice, and activate several intracellular signal transduction pathways, including stress and mitogen induced kinases (42).

It has been shown that vPK (ORF36) has protein kinase activity and is autophosphorylated on serine. The gene for ORF36 is expressed during lytic growth of the virus and has been classified as a late gene. ORF36 can activate the JNK pathway (19).

A family of alternatively-spliced transcripts is transcribed late in the lytic replication cycle from 8 exons located between ORF75 and the TR. This gene, K15, exists in two variants, in different viral isolates. The more common variant, K15-P, is considered to be the original K15 gene, whereas the other, K15-M, is thought to represent the result of a recombination event with a related rhadinovirus (16,22,30). K15 interacts with cellular proteins, TRAF (tumor necrosis factor receptor-associated factor) and Src kinases, and activates AP-1, NF-kappaB, and the mitogen-activated protein kinases (MAPKs) c-jun-N-terminal kinase and extracellular signal-regulated kinase (5). The downstream target genes of K15 signaling is determined using DNA oligonucleotide microarrays (6). K15 is shown to be able to induce expression of multiple cytokines and chemokines, including interleukin-8 (IL-8), IL-6, CCL20, CCL2, CXCL3, and IL-1alpha/

beta, as well as expression of Dscr1 and Cox-2 (6).

CONCLUSION

Kaposi's sarcoma-associated herpesvirus (KSHV) is the primary etiological agent of at least three malignancies associated with HIV infection and immunosupression: Kaposi's sarcoma, primary effusion lymphoma and multicentric Castleman's diseases. KSHV/HHV8 encodes a number of genes homologous to human genes involved in angiogenesis, anti-apoptosis and chemokine action, but has a very restricted gene expression pattern in KS and PEL. Many of the KSHV-regulatory genes may play a functional role in controlling cellular antiviral innate and adaptive immune response. These immune pathways might affect viral replication, regulate cell cycle, apoptosis and tumor cell immune surveillance. Some of the KSHV oncoproteins such as VIP, vIL-6, vIRF can also transform cells *in vitro*.

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