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Survey

Molecular piracy of Kaposi's sarcoma associated herpesvirus

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Abstract

Kaposi's Sarcoma associated Herpesvirus (KSHV) is the most recently discovered human tumor virus and is associated with the pathogenesis of Kaposi's sarcoma, primary effusion lymphoma, and Multicentric Casttleman's disease. KSHV contains numerous open reading frames with striking homology to cellular genes. These viral gene products play a variety of roles in KSHV-associated pathogenesis by disrupting cellular signal transduction pathways, which include interferon-mediated anti-viral responses, cytokine-regulated cell growth, apoptosis, and cell cycle control. In this review, we will attempt to cover our understanding of how viral proteins deregulate cellular signaling pathways, which ultimately contribute to the conversion of normal cells to cancerous cells. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Kaposi's sarcoma associated herpesvirus; Molecular piracy; Oncoprotein; Signal transduction; Immune evasion; Viral cytokine homologs; Viral antiapoptotic genes

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1. General background

For more than a century, Kaposis's sarcoma (KS) had been an interesting neoplasm only to a few clinicians due to its rare occurrence and very localized outbreaks primarily in Mediterranean white men. In addition, this complex proliferative lesion slowly progresses and presents with only mild clinical manifestation. The explosion of the AIDS epidemic around the mid 1980s brought increased attention to KS as it is the major malignancy amongst AIDS patients, occurring in approximately 20% of male HIV patients [1–3]. Great amounts of effort were put forth to increase our understanding of its etiology and pathology. An impressive linkage between KS and HIV initially led researchers to suspect HIV as the only and sufficient etiological cause for KS. The hunt for the causative agent came to an end and shifted to a new stage when Drs Chang and Moore discovered fragments of DNA specific to KS lesions that were similar to other known herpesvirus including Herpevirus saimiri (HVS) and Epstein-Barr virus (EBV) [4,5]. This new herpesvirus, named Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV8), was soon found in all epidemiological forms of KS, and indicated to be an etiologic agent of KS [6–11]. KSHV has also been identified in primary effusion lymphoma (PEL) and an immunoblast variant of Castleman's disease, which are of B cell origin [4,12,13]. Extensive studies have demonstrated that KSHV is present in spindle-shaped endothelial cells and infiltrating lymphocytes in KS tumors [6–11]. Serological and immunohistochemical assays also demonstrate that anti-KSHV antibodies against lytic and latent KSHV antigens are consistently present in groups at high risk for KS. Progression to KS has been shown to be preceded by KSHV seroconversion [14–16]. Although still limited, the presently available data provide compelling evidence that KSHV is a necessary cause for KS in HIV infected or other immunocompromised patients. However, this finding is not much of a surprise when one considers, as an analogy, the pathogenesis associated with EBV. In healthy individuals, EBV remains predominantly in a latent state with only a handful of genes being expressed without apparent symptoms [17,18]. However, individuals with congenital or acquired immunosupression have a higher risk for developing polyclonal lymphoproliferative disease or malignant B lymphomas.

This review will detail the molecular mechanisms of KSHV genes, whose roles are envisioned to contribute to the development of KS and PELs. Based on available information from other herpesviruses EBV and HVS, we will also attempt to describe the molecular mechanism of KSHV gene products in the alteration of cellular signal transduction pathways.

2. Related gamma herpesviruses

Gamma herpesviruses establish a life-long latent state primarily in lymphocytes until they are reactivated to replicate. Members of this group of viruses can be further divided into Gamma 1 and 2 herpesviruses, based on genomic sequence information [17]. EBV of both human and non-human primate origins belongs to Gamma 1 subgroup; KSHV, HVS, Rhesus monkey rhadinovirus (RRV), retinofibromatosis associated herpesviruses (RFHV) [19], and mouse herpesvirus 68 (MHV68) [20,21] fall into Gamma 2 subgroup.

2.1. Epstein-Barr virus (EBV)

Human EBV is able to transform lymphoid cells to growth factor-independent, permanent cell growth in culture and is responsible for various diseases [22–25]. These include Infectious Mononucleosis (IM), Burkitt's lymphoma (BL), Gastric Adenocarcinoma, Nasopharyngeal Carcinoma (NPC), Hodgkin's Disease (HD), non-Hodgkin's lymphoma, T cell lymphomas and the rare X-linked lymphoproliferative (XLP) disease [26–29].

Primary EBV infection is mostly asymptomatic in healthy individuals. However in individuals with an immunosuppressed condition, specific genetic alterations, or in certain environmental backgrounds, it can become clinically apparent with a wide range of symptoms including lymphadenopathy and fatigue (IM) [30,31], uncontrolled immunoblastic lymphomas (XLP) [32] and obstructive abdomen, ascites, hepatosplenomegaly (BL) [31]. Although most of the EBV genes are not essential for B-lymphocyte growth trans-

formation, deletion studies of individual EBV gene show that a subset of EBV genes, EBNA-LP, EBNA-2, EBNA-3A, EBNA-3C, LMP1 and possibly EBNA-1 are critical in B-lymphocyte transformation in culture. Functional roles of these EBV gene products have been described elsewhere [17,18,31].

2.2. *Herpesvirus saimiri (HVS)*

HVS is the best characterized Gamma-2 herpesvirus and shares a similar genomic organization with KSHV. HVS infects squirrel monkeys without an apparent disease. In other non-human primates, however, HVS induces rapidly progressing fatal T lymphoproliferative diseases [33–35]. Sequence divergence among HVS isolates is most extensive at the left end of the viral genome and is the basis for classification of HVS into subgroups A, B, and C [36]. Variation in this region is correlated with differences in the capacities of these viruses to immortalize primary T lymphocytes in vitro and to induce lymphoma in non-human primates [37–42]. Both subgroups A and C viruses immortalize common marmoset T lymphocytes to interleukin-2 (IL-2) independent proliferation [40,43]. However, none of subgroup B virus tested are capable of immortalizing common marmoset T lymphocytes. Furthermore, highly oncogenic subgroup C strains immortalize human, rabbit, and rhesus monkey lymphocytes and can produce fulminant lymphomas in rhesus monkeys as well as in rabbits [44–47]. Two HVS genes, STP (Saimiri Transforming Protein) and Tip (Tyrosine kinase-interacting protein), have been shown to be necessary for transformation. When each of them was deleted individually, the mutant viruses were not able to immortalize primary T lymphocytes in vitro and to induce lymphoma in marmosets [48]. Functional roles for HVS gene products including STP, Tip, vCyclin, vFLIP, vBcl-2 and vSag have been previously discussed in details [49].

2.3. *Rhesus monkey rhadinovirus (RRV)*

Recently, herpesvirus called rhesus monkey rhadinovirus (RRV) has been isolated that is closely related to but distinct from KSHV [50]. Two homologues of KSHV from different macaque species have also been identified in retroperitoneal fibromatosis [51]. These viruses were named retroperitoneal fibromatosis-associated herpesvirus from Macaca nemestrina (RFHVMn) and Macaca mulatta (RFHVMm). Complete DNA sequence analysis of RRV shows that RRV is much closer to KSHV than to HVS or other rhadinoviruses [52,53].

Unlike RRV and HVS, there is no efficient culture system for KSHV replication. Despite this difficult condition, numbers of groups have identified candidate genes of KSHV that appear to play critical roles in pathogenesis associated with this virus. Of these numerous ORFs, this review will feature KSHV genes: (1) which contain potential transforming activity; (2) which alter cellular signal transduction pathways; or (3) which modulate host immune responses (see details in Table 1).

3. Transformation related genes of KSHV

3.1. *K1*

At a position equivalent to HVS STP and the EBV LMP1 oncogene, KSHV contains a distinct open reading frame, called K1. The K1 gene is expressed at low levels in PEL and its expression is significantly induced during lytic viral replication [54]. The K1 protein is predicted to have a signal peptide sequence at the amino terminus, an extracellular domain, a transmembrane domain and a short cytoplasmic tail at the carboxyl terminus [55]. The predicted extracellular domain of the K1 protein demonstrates a regional homology in the primary amino acid sequence with the variable region of the lambda chain of the immunoglobulin light chain. In addition, similar to Ig-α and Ig-β, the cytoplasmic region of K1 contains a functional immunoreceptor tyrosine-based activation motif (ITAM) that is capable of eliciting signals to activate cellular signal transduction events [56,57]. Recently, Lee et al. have demonstrated that the amino terminal region of K1 specifically interacts with the μ chains of BCR complexes and this interaction retains BCR complexes in the endoplasmic reticulum, preventing their intracellular transport to the cell surface [58]. Thus, KSHV K1 resembles Ig-α and Ig-β in its ability to induce signaling and to interact with μ chains of the BCR. However, unlike Ig-α and Ig-β, which interact with μ chains to direct BCR complexes to the cell surface, K1 interacts with μ chains to block the intracellular transport of BCR complexes to the cell surface [58]. Expression of K1 in rodent fibroblasts induces both morphologic changes and focus formation, indicative of transformation [55]. Recombinant HVS carrying KSHV K1 in place of STP oncogene immortalizes primary T lymphocytes in vitro to IL-2 independent permanent cell growth and induces lymphoma in common marmosets [55]. Furthermore, a transgenic mouse study with the K1 gene has found that K1 expression induces a lymphoproliferative disease in several organs including kidney, lung and liver [unpublished data]. These findings further support a potential pathogenic role of K1 in lymphoproliferative diseases associated with this virus.

Table 1

ORF	Gene product	Experimental evidence	Putative function in infection or viral persistence	Possible role in KS pathogenesis	Expression pattern
K1	Transmembrane glycoprotein	Transformation in herpesvirus saimiri: lymphocyte immortalization, lymphoma induction ITAM signaling	Induce viral reactivation and amplification in infected host	Functional analog to other rhadinoviral oncoprotein	Productive
K2	Viral IL-6	Proliferation of B-cells, only gp 130 required	Control para/autocrine amplification in host	Paracrine growth stimulation of spindle cells	Productive
K3/K5	Zinc finger membrane protien	Downregulate MHC I, B7, ICAM-I	Immune evasion block CTL and NK activity	Persistent infection	Productive
vMIPs (K4, K4.1, K6)	Viral macrophage inflammatory proteins (vMIPs)	Binding to both CC and CXC receptors attraction of eosinophils induction of angiogenesis	Amplification in infected host	Angiogenesis	Productive
K9	Viral interferon response factor (vIRF)	Transformation, Inhibition of p300 and p53	Counteracting IFN-mediated antiviral activity	Interfering with the antiproliferative action of cellular IRF	Productive
K12	Kaposin A	Transformation	Unknown	Transformation	Latent
ORF16	vBcl-2	Anti-apoptotic activity, Bcl-2 and Bax binding	Counteracting elimination of persistently infected cells	Stabilizing productively infected cells	Productive
ORF71	vFLIP	Anti-apoptotic activity, FADD and TRADD binding	Counteracting elimination of persistently infected cells	Stabilizing latently infected cells	Latent
ORF72	vCyclin	Activates CDK6, resistant to CDK inhibitors, destabilizes p27	Proliferation of latently infected cells	Dysregulated cell cycle progression, inhibits cell cycle arrest	Latent
ORF74	vIL-8R	Constitutively active; induces VEGF secretion, transformation	Amplification in infected host	Angiogenesis, transformation of endothelial cells	Productive
K15	Integral membrane protein reminiscent of EBV LMP-2	Inhibit BCR Signaling, SH2 and SH3 binding	Block viral reactivation	Latent infection	Latent/productive

3.2. vIRF

Interferons (IFNs) are a family of cytokines that exhibit such diverse biological effects as the inhibition of cell growth and protection against viral infection. Viruses have evolved a variety of mechanisms to counteract the inhibitory effects of IFN [59]. E1A of adenovirus inhibits IFN-induced signaling by downregulating the expression of STAT-1 and ISGF3γ [60]. The terminal protein of hepatitis B virus also blocks the signaling by IFNs [61] and EBNA-2 of EBV inhibits IFN signaling by abolishing the induction of IFN-stimulated genes [62]. The major secreted protein (M-T7) of myxomavirus blocks IFN-signaling in a unique manner by binding IFN-γ and neutralizing its activity [59]. The KSHV K9 open reading frame exhibits significant sequence homology with cellular IFN regulatory factors (IRFs). We and others have demonstrated that expression of K9 dramatically represses transcriptional activation induced by IFN-$\alpha/\beta/\gamma$ [63–65]. Furthermore, K9 expression leads to transformation of rodent fibroblast cells, resulting in morphological change, focus formation, growth at reduced serum concentration, and tumor induction in nude mice [63,64]. Thus, the K9 gene of KSHV encodes the first viral interferon regulatory factor (vIRF) which functions as a repressor of cellular IFN-mediated signal transduction and as an oncogene to induce cell growth transformation. These functional activities of vIRF appear to be attributed in part by an interaction with and inhibition of p300 and p53 [66–68]. Interaction of vIRF with p300 displaces PCAF from p300 complexes and inhibits the histone acetyltransferase (HAT) activity of p300 in vitro and this in turn induces a dramatic hypoacetylation of nucleosomal histone H3 and H4 in vivo [66]. As a consequence, vIRF downregulates the transcriptional activity of the early inflammatory gene (IFNA) promoter [67], whereas it upregulates expression of cellular myc at the transcriptional level [68]. Thus, the modulation of p300 HAT activity is likely a part of the mechanism which vIRF employs to block cellular IFN-mediated anti-viral activity. Recently, we have also observed that vIRF interacts with the p53 tumor suppressor protein and this interaction results in a significant inhibition of p53-mediated transcriptional activation and apoptosis [unpublished result]. Thus, KSHV vIRF targets important cellular transcriptional factors to deregulate host anti-viral activity and to facilitate cell growth transformation.

3.3. Kaposin

The most abundantly expressed latent transcripts encoded by KSHV are derived from the genomic region surrounding open reading frame (ORF) K12 [69]. The 0.7kb transcript (T0.7) is detected by in situ hybridization in the majority of spindle cells during all stages of KS progression as well as in PEL cell lines [70–73]. The expression profile of the K12 locus displays a remarkable complexity with multiple potential transcriptional and translational initiation sites [69]. One form of the K12 gene encodes a 60 amino acid long hydrophobic protein, called Kaposin A, and its expression induces focus formation of rodent fibroblast cells and tumor formation in athymic nude mice [74,75]. Because of controversial nature of its expression, the potential role of Kaposin A in transformation remains to be tested in a more stringent assay system.

3.4. vGCR

The G-protein coupled receptors belong to a class of cellular receptors that are characterized by a uniform molecular architecture of seven transmembrane alpha-helices linked by extra- and intra-cellular peptide loops [76]. Binding of diverse agonists to these heptahelical receptors leads to a reversible activation of a limited repertoire of heterotrimeric guanine nucleotide-binding proteins (G proteins) forwarding the signal to intracellular effectors such as enzymes and ion channels [77].

KSHV encodes a G-protein-coupled receptor (vGCR) homologous to the human receptor for the angiogenic chemokine interleukin-8 (IL-8R) [78–80]. Competitive binding assays show that KSHV vGCR contains binding affinity to various CXC chemokines (IL-8, MGSA, NAP-2 and PF-4) and limited members of the CC chemokines (I-309 and RANTES) [81–83]. However, despite binding to a broad spectrum of chemokines, vGCR has been shown to be agoinst-independent, constitutively active and capable of eliciting signals to induce phosphoinositide-inositoltriphosphate/protein kinase C pathway [81,84]. Along with this finding, the N-terminal extracellular region of vGCR has been shown to be necessary for high affinity chemokine binding, but to be dispensable for its signaling activity [83]. In addition, while cellular G-protein coupled receptors require subunits of the heteromeric proteins G16(Gα16) or G15(Gα15) for its signal transduction, these heteromeric proteins are not required for transducing vGCR signaling [81]. This indicates that the signal transduction pathway of KSHV vGCR is significantly distinct from that of cellular GCRs.

Ectopic expression of vGCR in rodent kidney and fibroblast cells has been shown to elicit a constitutively active signal that strongly stimulates both proliferation and angiogenesis [81,85]. Bais et al., have shown that angiogenic responses induced by vGCR are mediated by upregulation of vascular endothelial growth factor (VEGF) [85]. Furthermore, upregulation of VEGF gene expression is mediated through JNK/SAPK and p38MAPK signal transduction pathways, characteristic of activation by inflammatory cytokines [85]. Despite

these remarkable properties, vGCR expression in KSHV-infected PEL cells and in KS tumors is mostly limited to the early phase of the viral lytic program [86–88]. This poses a dilemma for a potential role of vGCR in KS pathogenesis where the dominant population of KSHV infected-spindle cells is in a latent state. One plausible explanation might be that the lytic expression of vGCR acts through a paracrine mechanism to induce the upregulation of angiogenic growth factors VEGF and inflammatory cytokines, resulting in angiogenesis and infiltration of lymphocytes into the KS lesion [86]. In support of this hypothesis, KSHV GCR expression within the hematopoietic cell lineage of transgenic mice has been shown to result in the development of angioproliferative lesions in multiple organs that morphologically resemble KS lesions [89]. Thus, alteration of cellular signal transduction by vGCR may contribute to dysregulated angiogenesis and increased tumorigenecity of virus-containing cells.

3.5. vCyclin

Cyclins are regulatory subunits of a specific class of cellular kinases, called cyclin-dependent protein kinases (CDKs). Members of CDK family control the progression of cell division cycle through phosphorylating cellular substrates, including Rb tumor suppressor protein [90]. KSHV ORF72 has been shown to encode a G1 cyclin homolog, called viral cyclin (vCyclin), similar to cellular cyclin D2 and vCyclin expresses mostly in the latent state of viral replication [91–93]. Almost the same level of similarity can also be found at the amino acid level between KSHV vCyclin and a cyclin homolog encoded by HVS [91,92]. KSHV vCyclin protein has been shown to predominantly associate with CDK6, a cellular cyclin-dependent kinase known to interact with cellular type D cyclins and HVS vCyclin. Unlike cellular cyclin D-CDK6 complexes, however vCyclin-CDK6 complexes are resistant to CDK inhibitory proteins p16, p21cip1 and p27kip1 [94–96]. In fact, vCyclin-CDK6 kinase complexes are able to phosphorylate p27Kip1 inhibitor and to abolish its inhibitory effect by a concomitant destabilization and degradation [96]. In addition, X-ray crystal structural analysis of vCyclin demonstrates that the p27Kip1 binding area of vCyclin displays a very differently shaped surface than that of cellular cyclins, which accounts for the resistance of vCyclin complexes to CDK inhibitors [97]. While the significance of KSHV vCyclin in the viral life cycle remains speculative due to a lack of permissive cell culture system, these findings suggest that vCyclin could be part of mechanisms utilized by KSHV to deregulate cell growth control. This hypothesis is also supported by the fact that there is a correlation between the overexpression of cellular cyclins and some types of cancer [98,99].

4. Viral cytokine homologs

4.1. vMIP-I, vMIP-II and vMIP-III

The migration of leukocytes from blood vessels to sites of infection and inflammation is an important part of host defenses [100]. Chemokines are molecules that interact with G protein-coupled chemokine receptors and play a key role in leukocyte recruitment [101,102]. They have also been implicated in hematopoiesis, angiogenesis, and lymphocyte development [103]. Many viruses, particularly herpesviruses, have captured and modified cellular chemokine and chemokine receptor genes to modulate the host immune response [104]. Three open reading frames of KSHV, called vMIP-I, vMIP-II and vMIP-III, share 25–40% homology at the amino acid level with a CC chemokine, macrophage inflammatory protein α (MIP-1α) [105–108]. Among these, vMIP-II exhibits an unusually broad spectrum of receptor binding activities [109]. Competition assays have demonstrated that vMIP-II efficiently competes with cellular chemokines for binding to cellular chemokine receptors, including CC chemokine receptor 1(CCR1), CCR2, CCR5, CXCR4 and CX3CR1. However, unlike cellular chemokines, vMIP-II binding to these receptors does not elicit Ca^{++} influx, suggesting that the viral chemokine may function as a competitive antagonist. In fact, vMIP-II potently blocks the chemoattractive effects of both CC and CXC chemokines in vitro [107,109–111] and also significantly reduces the infiltration of inflammatory leukocytes and suppresses the onset of the host inflammatory response in a rat model [111]. The fact that expression of vMIP-I, vMIP-II and vMIP-III induces angiogenesis in the chorioalantonic membrane of chicken eggs [110] indicates that these viral chemokines, together with cellular angiogenic factors VEGF, bFGF and IL-6, may contribute to the development of angioneoplasms associated with KSHV [112].

4.2. vIL-6

Previously known as B-cell differentiating factor, interleukin-6 (IL-6) is expressed in lymphocytes, macrophages and endothelial cells. While it acts on most cells, it is particularly important in inducing B cells to differentiate into antibody-producing plasma cells and is considered to be an important growth factor for multiple myeloma, lymphoma, and leukemia. KSHV ORF K2, which has homology to human IL-6 at the amino acid level, is constitutively expressed in the latent/lytic stage of BCP-1 cells but only in the lytic stage of BC-1 cells [106,107]. Immunohistochemistry has shown that only a minor population of virus infected cells in KS lesions expresses vIL-6, whereas a high level of vIL-6 expression is detected in tissues from

Multicentric Castleman's disease, indicating a confined role of vIL-6 in KSHV-associated lymphoproliferative disorders [113,114].

Functional studies with cloned vIL-6 gene have demonstrated that it is able to support proliferation of an IL-6 dependent mouse myeloma cell line and to promote the growth of KSHV infected PEL cells [106,107,114]. It also promotes hematopoiesis and acts as an angiogenic factor through the induction of VEGF [115]. Despite their similarities in sequence and function, cellular IL-6 and vIL-6 display differences in receptor usage. While cellular IL-6 requires both IL-6R and gp130 for intracellular signaling, vIL-6 appears to bind to only gp130, and this binding is sufficient to elicit its signal transduction [116,117]. In addition, vIL-6 has been shown to activate Janus kinase 1, STAT-1/3, and MAPK in both MH60 and B9 cells [116,118,119]. Thus, vIL-6 is a multifunctional cytokine that potentially contributes to KSHV-associated lymphoproliferative diseases by constitutively activating the gp130-JAK kinase-MAPK signal transduction pathway and by preventing apoptosis of virus-infected cells.

5. Modulators of immune responses

5.1. K3 and K5

The early stage of viral infection, there is a race between the virus and the host's defense system which are mediated through: (1) early non-specific or innate immune defenses such as interferon, natural killer (NK) cells and macrophages; (2) specific or adaptive immune responses by cytotoxic T lymphocytes, helper-T lymphocytes, and anti-viral antibody [120]. Downregulation of the cell surface MHC class I molecules has been a critical tool of immune evasion employed by human and animal viruses [120]. Herpesviruses encode a variety of proteins that function to lower MHC I display by several mechanisms. These include binding and retention of MHC I chains in the endoplasmic reticulum, dislocation of class I chains from the ER, inhibition of the peptide transporter TAP involved in antigen presentation, and shunting of newly assembled chains to lysosomes [121–124].

KSHV encodes the K3 and K5 zinc finger membrane proteins that exhibit 40% amino acid identity to each other and are expressed during early lytic cycle of viral replication [125,126]. Recently, we and others have reported that the K3 and K5 proteins dramatically downregulate surface expression of MHC class I molecules [127,128]. Biochemical analyses have demonstrated that while K3 and K5 do not affect expression and intracellular transport of class I molecules, their expression induces rapid endocytosis of class I molecules [127,128]. Despite their similarity in sequence and function, K3 and K5 differ in their specificity as K3 drastically downregulates HLA-A, -B, -C and -E, whereas K5 exclusively downregulates HLA-A and -B [128]. This selective downregulation of HLA allotypes by K5 is partly due to differences in the amino acid sequences of the HLA transmembrane regions. Although MHC class I downregulation may protect KSHV-infected cells from cytotoxic T lymphocyte recognition, indiscriminate downregulation of HLA allotypes by K3 invites natural killer cell susceptibility [129]. To prevent this, K5 additionally downregulates ICAM-1 and B7-2, which are ligands for NK cell-mediated cytotoxicity receptors [129]. As a consequence, K5 expression drastically inhibits NK cell-mediated cytotoxicity. This is a novel viral immune evasion strategy where KSHV achieves immune avoidance by downregulation of cellular ligands for NK cell-mediated cytotoxicity receptors [129]. Thus, KSHV uses two genes, K3 and K5, with similar but distinct activities to ensure comprehensive protection from host immune effectors

6. Antiapoptotic viral genes

Upon viral infection, the infected cells can become the target of host immune responses or can go through a programmed cell death process, called apoptosis, as a defense mechanism to limit the ability of the virus to replicate. To prevent this, viruses have evolved elaborate mechanisms to subvert the apoptotic process to facilitate a persistent infection or prolong the survival of lytically infected cells to maximize the production of viral progeny. Most of the DNA viruses including KSHV are genetically equipped to prevent cellular apoptosis. Specifically, KSHV contains two anti-apoptotic genes, vFLIP and vBCL2.

6.1. vFLIP

ORF K13 of KSHV encodes viral FLIP (vFLIP), a homologue of the cellular FLICE (Fas-associated death domain-like interleukin 1 beta-converting enzyme) inhibitory protein (FLIP). KSHV vFLIP has been shown to protect cells from Fas/APO1-mediated apoptosis by inhibiting activation of caspase -3, -8, -9 and also permits clonal growth in the presence of death stimuli in vitro [130]. Moreover, vFLIP has also been shown to modulate the NF-KB signaling pathway through association with TRAFs and downstream signaling proteins [131]. Transcripts from the locus comprising vFLIP, vCyclin and ORF73 (LANA) appear to be differentially spliced in PEL cell lines, KS lesions, and lymph nodes. vFLIP is expressed at very low level in early KS lesion with expression increasing dramatically in late-stage lesions [132]. In addition, the increase in the amount of vFLIP transcripts is associated with a reduction in

apoptosis in KS lesions, suggesting a possibility that functional vFLIP protein may be expressed in vivo.

6.2. vBCL-2

While the overall amino acid sequence identity of KSHV ORF16 to cellular Bcl-2 is only 15–20%, it contains the BH1 and BH2 regions required for heterodimerization of Bcl-2 and for its death-repressor activity. vBcl-2 is expressed in both classical- and AIDS-KS lesions and in cell lines derived from primary effusion lymphomas [133]. Over-expression of vBcl-2 has been shown to block apoptosis as efficiently as cellular Bcl-2, Bcl-xL, or another viral Bcl-2 homolog encoded by Epstein-Barr virus, BHRF1 [134]. In addition, vBcl-2 has been shown to block Bax-mediated toxicity in yeast [133]. While the ability of vBCL-2 to heterodimerize with the cellular Bcl-2 family is controversial, it is now clear that KSHV pirates cellular anti-apoptotic gene to escape negative regulatory effects on viral infection and replication.

7. Conclusion

Historically, DNA tumor viruses have been essential tools in the analysis of cellular pathways involving signal transduction, transcriptional regulation and transformation. Many tumor viruses stimulate the proliferation of the infected cells. The analysis of viral genes associated with transformation has revealed many different strategies by which viruses achieve this end. Like other DNA tumor viruses, KSHV encodes a diverse array of viral genes that contribute to converting normal cell growth to cancerous cell growth. By using unique viral genes and counterparts to cellular genes, KSHV deregulates normal cellular pathways that, otherwise, lead to apoptosis, activation of the host immune system, and cell growth arrest.

Soon after KSHV infection through a route yet to be deciphered, there must be an intensive race between virus to spread to uninfected cells and the host's immune system. The outcomes of this race will depends on how rapidly the virus can infect and/or replicate before it is cleared by an efficient immune system. The virus attempts to handicap the race in its favor by encoding various proteins that allow it to escape host immune surveillance. Thus, the success of a persistent virus infection lies in its capacities for the evasion of host defense mechanisms by inhibiting the function of cellular proteins that are important components of host immune response. To achieve persistent infection, KSHV has evolved elaborate mechanisms that target and modulate different aspects of the host's immune system. It contains unique genes; K3 and K5 that comprehensively inhibit host immune effectors, vIRF that suppresses IFN-mediated immune response, and vFLIP and vBcl-2 that inhibit the apoptosis-mediated host defense mechanism. In addition, both K1 and K15 [135] have been shown to modulate the B cell receptor

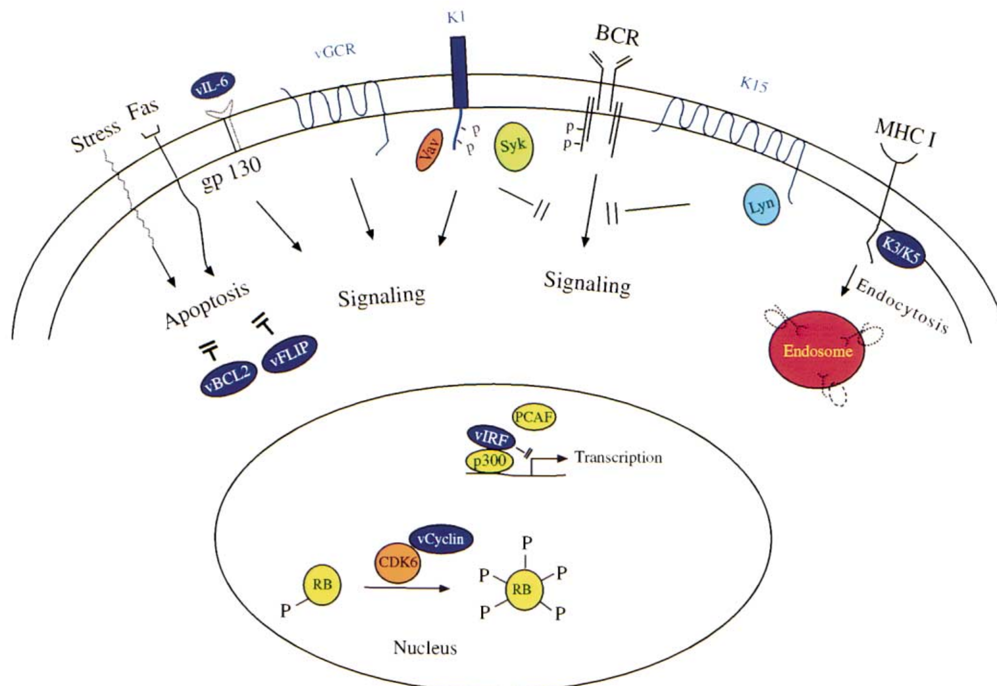

Fig. 1. Alteration of cellular signal transduction pathways by KSHV proteins. KSHV viral gene products are indicated by blue-colored box or letter. Each viral protein has been described in the text. → indicates 'activation of pathway' and –‖ indicates 'inhibition' of pathway.

signaling, through disruption of surface presentation of BCR complex or by sequestering cellular signaling proteins critical for BCR function, which otherwise induce apoptosis of infected cells or antiviral responses [Fig. 1]. On the other hand, the capability of KSHV to express vMIP -1, -2, -3 and vIL-6 along with vGCR may allow the virus to induce autocrine/paracrine mechanisms of cellular signal transduction to promote deregulated cell growth [Fig. 1].

We have witnessed in recent years the dissection and molecular characterization of individual KSHV gene products and have come to have a better understanding of molecular mechanisms that underlie the pathogenesis associated with this virus. Amongst more than 80 open reading frames predicted in the KSHV genome, four gene products including K1, K9, K12 and vGCR have been shown to have transforming activity in cell culture. In addition, vCyclin, vFLIP, and vBcl-2 have been shown to deregulate cell cycle control and programmed cell death in defined conditions. However, we are still deficient in our understanding of the contribution of these gene products to KS progression and lymphomagenesis in vivo. Thus, we are getting to a stage where better genetic tools and pathogenic animal models are needed to elucidate in vivo functional roles of viral gene products in diseases associated with KSHV. Fortunately, several animal homologs of KSHV that have efficient cell culture system have been identified and well characterized for the study of viral replication and pathogenesis. These include rhesus monkey rhadinovirus (RRV), herpesvirus saimiri (HVS), and mouse herpesvirus 68 (MHV68). Detailed studies with these KSHV homologs in animals will provide a new insight into understanding the molecular mechanisms of viral pathogenesis.

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