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MINIREVIEW

Signaling Activities of Gammaherpesvirus Membrane Proteins

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Members of the *Herpesviridae* family have large double-stranded DNA genomes and replicate in the nucleus of the host cell. Based on genomic organization and biological characteristics, herpesviruses are classified into three subfamilies: alpha, beta, and gamma (Fig. 1A). The gammaherpesviruses replicate and persist in lymphoid cells, but some are capable of undergoing lytic replication in epithelial or fibroblast cells. These viruses can be subdivided into two genera: lymphocryptoviruses (gamma-1) and rhadinoviruses (gamma-2) (Fig. 1A). The lymphocryptoviruses (gamma-1) include *Epstein-Barr virus* (EBV) or *Human herpesvirus 4*, *Lymphocryptovirus of rhesus monkeys*, and *Herpesvirus papio* of baboons, whereas the rhadinoviruses (gamma-2) include *Herpesvirus saimiri* (HVS), *Kaposi's sarcoma-associated herpesvirus* (KSHV) or *Human herpesvirus 8*, *Rhesus monkey rhadinovirus* (RRV), *Equine herpesvirus 2*, and *Mouse herpesvirus 68* (Fig. 1B).

The gammaherpesviruses, including HVS, EBV, KSHV, and RRV, are capable of establishing latent infection in lymphocytes. Both HVS and EBV have also been shown to transform lymphoid cells and to induce lymphoproliferative diseases in the natural or experimental host. EBV has been shown to be associated with several diseases in humans (16, 40, 78). These include infectious mononucleosis (IM), Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), Hodgkin's disease (HD), and T-cell lymphomas (1, 11, 65, 83, 84, 95, 96, 108, 116, 141). Primary EBV infection is usually asymptomatic, but a proportion of EBV-infected individuals develop IM, a disease characterized by lymphadenopathy and fatigue, later in life. A rare disease called fatal IM or X-linked lymphoproliferative (XLP) syndrome is an EBV-dependent malignancy characterized by uncontrolled immunoblastic lymphomas which are consistently EBV positive (115). The genetic defect in XLP is in the SLAM-associated protein, SAP. The mutated SAP protein in XLP patients affects T/B-cell interactions induced by SLAM, leading to an inability to control the B-cell proliferation caused by EBV infections (123, 133). BL is a malignancy that principally affects children, especially those that live in regions of Africa with a high incidence of malaria (16). The tumor cells of these lymphomas are closely associated with EBV, with 100% of the lymphomas scoring positive for EBV. In other areas of the world, however, the occurrence of BL is more sporadic and a lower percentage of these lymphomas are EBV positive (65). BL is characterized by distinct chromosomal translocations of the c-*myc* oncogene and immunoglobulin promoter sequences, resulting in the deregulation of c-*myc* expression (23). Another EBV-associated disease is NPC, a malignancy of the squamous epithelium situated in the nasopharynx (117). EBV is consistently present in cases of epithelial dysplasia, and it is thought to have arisen from clonal expansion of latently infected cells (113, 116). The incidence of NPC is high in Southern China, Northern Africa, and Eskimo populations. HD is the most common malignancy in the Western world, with about 30 to 90% of all HD lymphomas being EBV positive. Like NPC, the EBV genomes in these tumor cells are monoclonal (139). EBV is also present in about 70% of all immunoblastic lymphomas in human immunodeficiency virus (HIV)-infected individuals and in 100% of immunoblastic lymphomas of immune-suppressed posttransplant patients. Recently, EBV, a primarily B-cell-tropic virus, has been detected in different types of human T-cell lymphomas. About 100% of all nasal T-cell lymphomas in Southeast Asia and 100% of T-cell tumors in XLP males contain EBV (65).

Epidemiological studies from many laboratories, using antibody prevalence assays, PCR, and immunohistochemistry, suggest that KSHV is the etiologic agent responsible for Kaposi's sarcoma (KS). KSHV DNA sequences have been widely identified in KS tumors from HIV-positive and HIV-negative patients (20, 93, 132). KSHV has also consistently been found in specific lymphoproliferative diseases such as body cavity-based lymphomas (BCBLs), also called pleural effusion lymphomas, and lymphoblastic variants of multicentric Castleman's disease (MCD) (17, 46, 102, 112, 130). These are principally or exclusively of B-cell origin. There are reasons to believe that the abnormal cell proliferation in KS may differ from the traditional virus-transformed cell paradigms of other transforming viruses. The KS lesion has a mixed cell phenotype. One unusual cell consistently present, and thought to be critical, is a spindle-shaped cell believed to be of endothelial origin. While cells cultured from KS lesions do not contain KSHV, spindle cells in the KS lesion do contain KSHV genetic information. Several studies have suggested a high level of cytokines and chemokines within KS lesions and a dependence on these cytokines and chemokines for maintenance of the lesion (20, 106). BCBLs were first identified in patients with AIDS and were later found to have a high incidence of EBV and KSHV coinfection, although some lymphomas were only positive for KSHV (17, 69). BCBLs are thought to be monoclonal in origin and lack many B-lymphocyte antigens like CD19, CD20, and cell homing and adhesion markers (13, 34). MCD is an atypical lymphoproliferative disorder that includes hyperplasia, lymphadenopathy, and splenomegaly. Both HIV-infected and -uninfected individuals develop MCD, although there is a high rate of KSHV infection in the lymph nodes of HIV patients with MCD (18, 66, 130). It has been demonstrated that viral interleukin-6 (IL-6) acts as an autocrine or paracrine factor in the lymphoproliferative processes common to both BCBLs and MCD (111, 131). In addition, KSHV has been shown to im-

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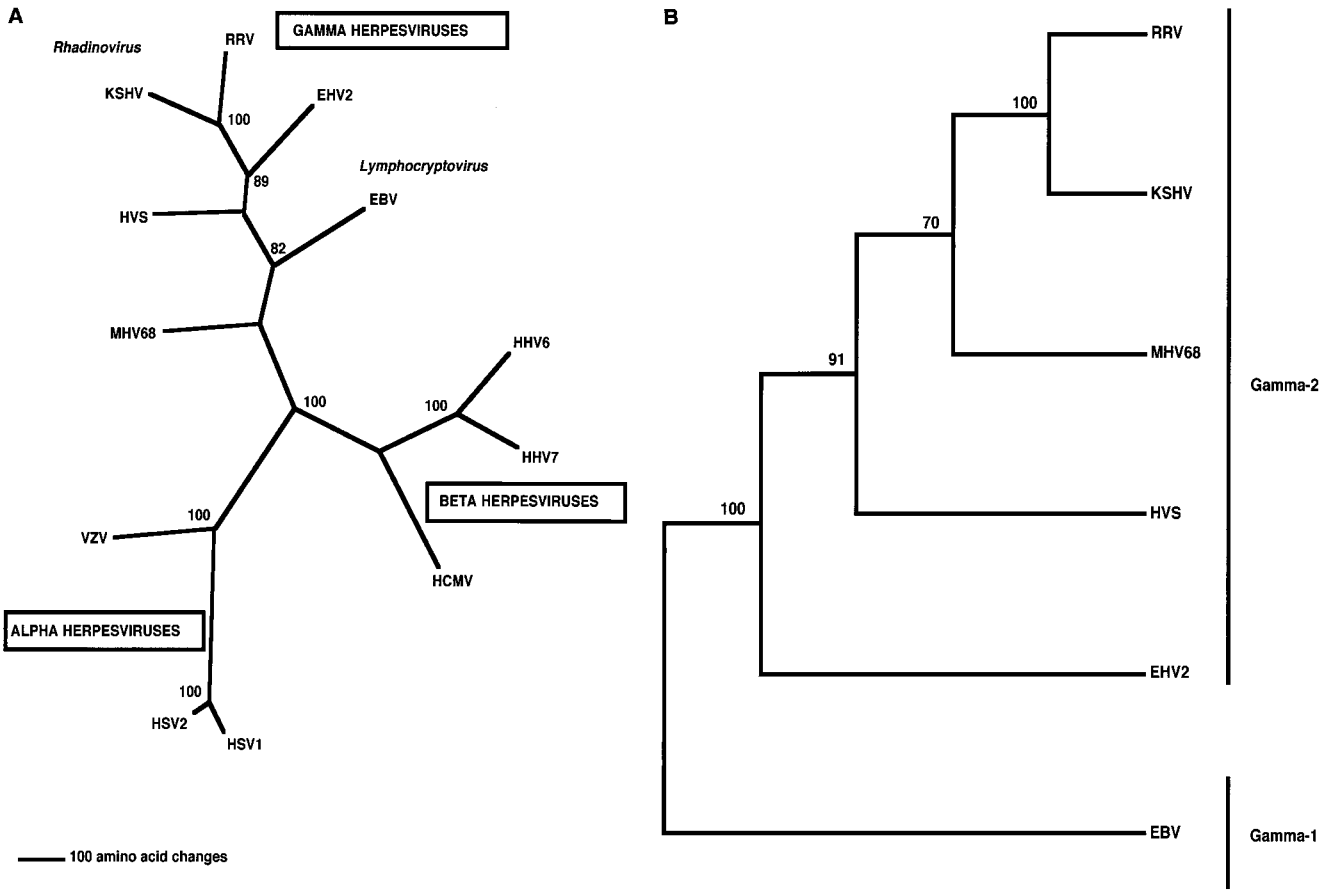

FIG. 1. Classification of herpesviruses. (A) Phylogenetic tree depicting the three subfamilies of herpesviruses: alpha, beta, and gamma. The phylogram was constructed using the viral DNA polymerase gene by parsimony analysis with the neighbor-joining method. The number of amino acid changes can be determined using the scale shown at the bottom of the tree. (B) Cladogram of the gammaherpesvirus subfamilies. A cladogram of gamma-1 (lymphocryptoviruses) and gamma-2 (rhadinoviruses) herpesviruses was constructed by using the conserved glycoprotein B (gB) gene and a distance analysis. HHV6 and -7, human herpesvirus 6 and 7; MHV68, mouse herpesvirus 68.

mortalize primary human endothelial cells to long-term proliferation and survival (43). Interestingly, KSHV is found to be present in only a subset of cells, and paracrine mechanisms have been shown to be responsible for the survival of uninfected cells (43).

Recently, a herpesvirus called RRV was isolated that is related to but distinct from KSHV (30). Two homologues of KSHV from two different macaque species have also been identified in retroperitoneal fibromatosis (119). RRV replicates lytically and to high titers in cultured rhesus monkey fibroblasts. Complete DNA sequence analysis of this virus shows that it is much closer to KSHV than to HVS or other rhadinoviruses (4a, 127). A serological study showed that over 95% of rhesus monkeys are strongly positive for the presence of antibodies to this herpesvirus, suggesting that rhesus monkeys are a natural host for RRV infection (31). While specific diseases associated with RRV remain to be determined, some of the naïve seronegative rhesus macaques inoculated with RRV developed lymphadenopathy and vascular hyperplasia (85, 140) similar to that observed in KSHV-infected men (18, 66, 130). Furthermore, inoculated monkeys remained persistently infected with RRV (85).

HVS resides in the T lymphocytes of its natural host, the squirrel monkey, without causing any disease (29). However, HVS infection of other New World primates, e.g., common marmosets, tamarins, and owl monkeys, results in rapidly progressing lymphomas, lymphosarcomas, and leukemias (26, 27, 41). Subgroups A and C are highly oncogenic and are able to immortalize common marmoset T lymphocytes to IL-2-independent growth in vitro (27, 35, 62). In addition, HVS subgroup C is further capable of immortalizing human, rabbit, and rhesus monkey lymphocytes into continuously proliferating T-cell lines (2, 8, 35, 91). Because of the presence of a permissive cell culture system and in vitro and in vivo transformation assays, HVS provides a unique opportunity to investigate the mechanisms of cancer induction by oncogenic herpesviruses.

Gammaherpesviruses share an ability to transform lymphocytes in natural or experimental hosts. The correlation between gammaherpesviruses and disease induction in primates enables a study of the contributions of individual herpesvirus genes to cell growth transformation in a meaningful fashion. A striking feature of these four gammaherpesviruses is that they contain distinct open reading frames (ORFs) at the left and right ends of their respective genomes. Each of these ORFs is involved in lymphocyte signaling events. At the left end of each viral genome are located ORFs encoding distinct transforming proteins. These include the saimiri transformation protein (STP) of HVS, latent membrane protein 1 (LMP1) of EBV, K1 of KSHV, and R1 of RRV. These proteins do not share sequence relatedness, with the exception of limited structural homology between R1 and K1, which is reflective of the fact that RRV is the rhesus homologue of KSHV. In addition, the STP, LMP1,

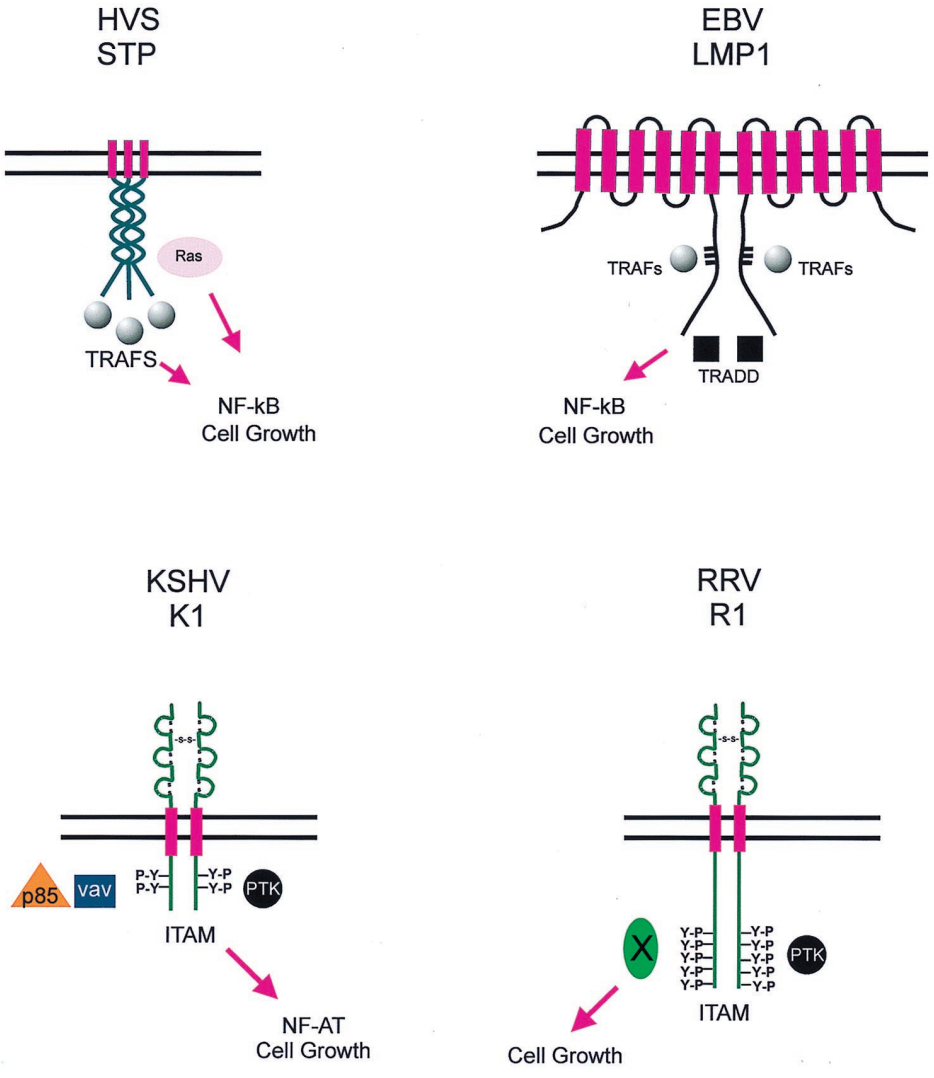

FIG. 2. Schematic representation of the LMP1, STP, K1, and R1 proteins. Interactions with cellular partners and activation of cellular pathways are indicated. Y-P represents the presence of phosphorylated tyrosine residues in K1 and R1.

and K1 proteins show high sequence divergence among individual isolates from the same species (29, 31, 63, 71, 103, 105, 107, 143). This may be a consequence of their proximity to the terminal repeats of the viral genome, a region of high mutagenicity arising from the fact that these repetitive sequences undergo homologous recombination at an increased frequency. In contrast, in a limited survey, the R1 protein did not appear to be highly divergent (24, 127).

EBV LMP1

EBV was the first human gammaherpesvirus to be discovered and hence has been studied extensively. The first ORF of EBV encodes a well-characterized transforming protein, LMP1. The LMP1 protein has six transmembrane-spanning domains and a 199-amino-acid cytoplasmic domain. LMP1 has been shown to transform rodent fibroblasts and to be essential for the immortalization of primary B lymphocytes to lymphoblastoid cell lines (5, 137, 138). LMP1 has recently been shown to mimic the B-lymphocyte activation antigen CD40 (47, 53, 67). Like CD40 and other members of the tumor necrosis factor (TNF) receptors, the carboxy-terminal domain of LMP1 is capable of interacting with TNF receptor-associated factors (TRAFs) and with the TNF receptor-associated death domain (TRADD) (32, 33, 37, 38, 56, 122) (Fig. 2). The interaction of LMP1 with TRAFs and TRADD has been shown to be essential for the activation of the NF-κB pathway and for EBV-induced immortalization of B lymphocytes (56, 57, 64). However, unlike CD40, the transduction of signals occurs in the absence of extracellular ligands or cross-linking. This is caused by multimerization of the LMP1 protein through its transmembrane domains, a property that mimics ligand-induced CD40 receptor aggregation (Fig. 2). Multimerization generates a constitutively active signal that results in pleiotropic effects, including the activation of NF-κB and JNK activity, and induction of *bcl-2*, *bclx*, *mcl1*, and *A20* gene expression (37, 39, 42, 53–57, 73). Hence, by mimicking the function of the B-lymphocyte CD40 receptor, LMP1 contributes to EBV-induced transformation of B lymphocytes.

HVS STP

Before the discovery of KSHV, HVS had been the most extensively studied gamma-2 herpesvirus (58). Based on the

extent of sequence divergence at the left end of the HVS genome, the virus has been further classified into subgroups A, B, and C (86). Subgroup A and C strains immortalize common marmoset lymphocytes, but none of the subgroup B strains scored positive in in vitro immortalization assays. The first ORF of the HVS genome codes for highly related STPs in all three subgroups (27, 28, 70, 99). Deletion of the STP genes from subgroup A and C viruses results in viruses that are capable of replication but unable to induce lymphomas in common marmosets and unable to transform primary T lymphocytes in vitro (35, 99). STPs of HVS subgroups A and C have transforming and tumor-inducing activities independent of those of the rest of the herpesvirus genome. Specifically, the STP of HVS subgroup C, STP-C, can transform Rat-1 cells, resulting in apparent loss of contact inhibition, formation of foci, growth at reduced serum concentrations, and formation of invasive tumors in nude mice. The STP of HVS subgroup A, STP-A, is less potent than STP-C in its transforming ability. Furthermore, transgenic mice expressing STP-A developed peripheral pleomorphic T-cell lymphomas, while transgenic mice expressing STP-C developed extensive epithelial cell tumors (62, 99).

Both STP-A and STP-C proteins are predicted to have three distinct domains: an acidic amino terminus, collagen-like repeats in the central region, and a hydrophobic carboxy terminus (Fig. 2). The primary amino acid sequence of STP-A11 has nine copies of a collagen-like motif (Gly-X-Y, where X and/or Y is a proline residue) that are not contiguous. In STP-C488, it is directly repeated 18 times and comprises more than 50% of the protein. These collagen-like repeats are found to be a primary determinant for the transforming activity of the STP gene (J. K. Choi and J. U. Jung, unpublished data). STP-A and STP-C also contain a hydrophobic stretch at their carboxy termini sufficient for a membrane-spanning domain.

As a result of its essential role in HVS transformation, STP-C has been extensively studied. It has been shown to associate with cellular Ras (59), and this interaction is critical for its transforming activity in cell culture (Fig. 2). Furthermore, oncogenic v-*ras* can complement the HVS STP oncogene to induce lymphocyte transformation and does so more efficiently than normal c-*ras* (52). STP-C has also been shown to activate NF-κB transcriptional activity by interacting with TRAFs 1, 2, and 3 (75) (Fig. 2). While STP-A can also interact with these TRAFs, it is unable to upregulate NF-κB transcriptional activity (75). To add more complexity, STP-A does not interact with Ras but interacts with Src family kinases through its SH2 binding motif, YAEV/I (74). However, the potential role for the Src-STP-A interaction in transformation remains to be elucidated.

KSHV K1

At a position equivalent to that of the STP of HVS and the LMP1 of EBV, KSHV contains a distinct ORF called K1 (71, 77, 143). K1 is a 46-kDa transmembrane glycoprotein. Sequence analysis has recently demonstrated that the K1 gene is extremely variable, showing as much as 40% divergence at the amino acid level (143). While the amino-terminal extracellular domain of K1 is extremely variable, the carboxy-terminal short cytoplasmic tail is relatively well conserved (63, 77, 103, 143). This carboxy-terminal cytoplasmic tail contains a functional immunoreceptor tyrosine-based activation motif (ITAM) (72, 76) (Fig. 2). The ITAM is capable of transducing signals to induce cellular activation, calcium mobilization, and tyrosine phosphorylation, events that are indicative of lymphocyte activation (72, 76). However, unlike other ITAM-based signal transduction events which require a ligand-receptor interaction, K1 signaling appears to occur constitutively (72). The K1 protein has been shown to interact with several cellular signal transduction proteins that include Vav, p85 and Syk kinase (76) and to induce nuclear factor of activated T cells (NFAT) activity (72) (Fig. 2). In addition to the transformation of rodent fibroblasts, K1 can also functionally replace STP in HVS for the immortalization of common marmoset T lymphocytes to IL-2-independent growth and for the induction of lymphomas in common marmosets (77).

RRV R1

Like that of KSHV, the first ORF of the RRV genome also encodes a transforming gene, R1 (24). R1 shows limited sequence homology to K1 in its extracellular domain. The amino-terminal extracellular domains of both K1 and R1 closely resemble those of members of the immunoglobulin receptor superfamily (24, 77). R1 has also been shown to transform rodent fibroblasts and to functionally replace STP-C of HVS in immortalizing common marmoset peripheral blood mononuclear cells to IL-2-independent growth in vitro (24). Injection of R1-expressing rodent fibroblasts into nude mice resulted in the formation of multifocal and disseminated tumors in these mice (24). While the extracellular domains of R1 and K1 structurally resemble each other, the cytoplasmic tail of R1 is significantly longer than that of K1 and contains several potential SH2 binding motifs which function as ITAMs (Fig. 2) (24a). Further biochemical studies are needed to determine the detailed mechanisms of the alteration of cellular signaling pathways by R1 and K1 and their contribution to virus-induced cell growth transformation.

With the exception of the HVS tyrosine kinase-interacting protein (Tip) gene which is expressed as a bicistronic transcript with STP in HVS subgroup C, the genes for EBV LMP2a, KSHV K15, and RRV R15 are located at the right ends of the viral genomes. The LMP2a, K15, and Tip proteins are all capable of associating with the major B- or T-cell receptor-associated kinases and blocking their signaling activity. Cross-linking of the B-cell antigen receptor (BCR) and the T-cell antigen receptor (TCR) triggers a signal transduction cascade that leads to the activation of B and T lymphocytes, respectively. The EBV LMP2a, KSHV K15, and HVS Tip proteins can antagonize these signaling events, thus potentially preventing the reactivation of viral lytic infection from latently infected cells.

EBV LMP2A

LMP2a is expressed in B cells latently infected with EBV. LMP2a contains 12 transmembrane domains linked by loops and a short stretch of amino-terminal and carboxy-terminal domains (Fig. 3). LMP2a is expressed in aggregates in the plasma membranes of latently infected B cells. The amino-terminal cytoplasmic region of LMP2a has been shown to contain three tyrosine-based SH2 domain binding sites, two of which form a functional ITAM (45). This motif is tyrosine phosphorylated and is required for LMP2a association with the SH2 domain of the Lyn, Fyn, Syk, and Csk kinases (Fig. 3) (15, 79, 124). This interaction has been shown to be necessary for intracellular calcium mobilization and cytokine production by LMP2a (7). It has also been suggested that LMP2a is phosphorylated at serine residues by MAP kinases (109). While LMP2a is dispensable for EBV immortalization of B lymphocytes (80–82), its expression blocks normal BCR signaling in

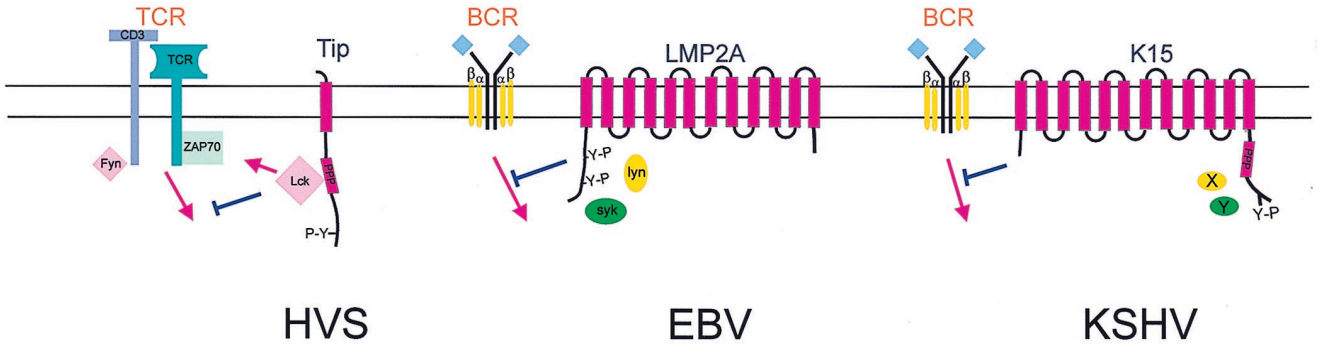

FIG. 3. Schematic representation of the LMP2a, Tip, and K15 proteins. Interactions with cellular partners and activation of cellular pathways are indicated. Y-P represents the presence of phosphorylated tyrosine residues in these proteins. Blue-colored T-bar, blocking of signal transduction.

EBV-negative B cells (90). In addition, studies using EBV-positive B lymphocytes have shown that this signaling block prevents the reactivation of lytic replication, indicating that EBV LMP2a may play a significant role in the establishment and maintenance of viral latency in vivo (88, 89).

HVS TIP

The HVS Tip gene is only present in HVS subgroup C virus, not in HVS subgroups A and B. HVS Tip has been shown to associate with a major T-cell tyrosine kinase, Lck, and this interaction inhibits the TCR-mediated signal transduction pathway (Fig. 3). Two motifs of Tip are responsible for interacting with Lck. These include the carboxy-termini of Src-family kinases (CSKH) motif and the SH3 binding motif (60, 61). Cell lines stably expressing Tip show a reduced level of TCR signal transduction (61). This negative effect on Lck-mediated TCR signal transduction has been shown to be enhanced by a point mutation in Tip which enhances Lck-binding affinity (51). In contrast, a mutation in the Lck-binding motif of Tip that abolishes Lck binding augments the transforming activity of HVS C488 in vitro and in vivo (36). This suggests that an interaction of Tip with Lck modulates the transforming ability of HVS. In addition, Tip has been shown to interact with the nuclear RNA export factor, Tap (Tip-associated factor), independently of Lck binding (49, 142). Expression of Tip and Tap in T cells upregulates surface expression of cellular adhesion molecules, leading to lymphocyte aggregation (142). However, the relevance of the Tip-Tap association for viral transformation remains to be elucidated.

KSHV K15

KSHV encodes a distinct ORF called K15 or latency-associated membrane protein (LAMP) which is located in the same genomic position as the EBV LMP2a (22, 48, 114). While K15 isolates exhibit a complex splicing pattern, they all consist of 4 to 12 transmembrane spanning domains and a short stretch of cytoplasmic domain (Fig. 3) (22, 48, 114). K15 is weakly expressed in latently infected BCBLs, and the level of its expression was significantly increased by tetradecanoyl phorbol acetate stimulation (22, 48). K15 proteins from different KSHV isolates exhibit dramatic sequence variation, showing as much as 60 to 70% divergence at the amino acid level (114). Like EBV LMP2a, the cytoplasmic domain of K15 contains signaling motifs that are highly conserved in most isolates (114). These include potential SH2 and SH3 binding motifs and a YASIL sequence (20, 48, 114). The cytoplasmic domain of K15 is constitutively tyrosine phosphorylated, and the tyrosine residue within the putative SH2 binding motif is a major site of phosphorylation by cellular tyrosine kinases (22). In addition, experiments with CD8-K15 chimeras demonstrate that unlike that of EBV LMP2a, the cytoplasmic domain of K15 is unable to elicit cellular signal transduction upon antibody stimulation. However, like EBV LMP2a, it is capable of inhibiting BCR signal transduction (22). Thus KSHV K15 is likely to be a distant evolutionary relative of EBV LMP2a.

RRV contains a gene named R15 at a genomic location equivalent to that of KSHV K15. R15 also contains multiple transmembrane domains and a cytoplasmic tail containing signal-transducing motifs (unpublished data). The functional role of R15 remains to be deciphered.

FUNCTIONAL COMMONALTIES

Except for the limited homology of the structural motifs seen between KSHV K1 and RRV R1, there is no discernible homology between the proteins encoded by the first ORFs at the left ends of the gammaherpesvirus genomes. The most interesting property they share is their ability to self-oligomerize (Fig. 2). EBV LMP1 has been shown to aggregate through its membrane-spanning domains, mimicking a ligand-induced activated CD40 receptor (47, 67). KSHV K1 and RRV R1 have also been shown to oligomerize through disulfide bonding of their extracellular domains (24, 71, 76, 77). The STP-C protein is capable of oligomerizing through its collagen repeats, and the integrity of this domain has been demonstrated to be essential for the transforming function of the protein (59; Choi et al., unpublished data). However, as an alternative, oligomerization of these proteins may be caused by endogenous ligands. In addition, both LMP-1 and STP-C488 can activate the NF-κB pathway through the binding of TRAFs (32, 33, 37, 38, 57, 75, 122), while the K1 and R1 proteins interact with Syk, a B-cell specific kinase, to induce cellular tyrosine phosphorylation and B-cell activation events (24a, 72, 76). Thus, these proteins share the ability to interact with host factors and to activate cellular signaling pathways. Such similarities exist in the lack of any discernible sequence homology as to imply that these first ORFs are not ancestral herpesvirus genes but have been recently acquired by the individual viral genomes. In either event, through self- or ligand-induced oligomerization and interaction with host cellular factors, these viral transforming proteins appear to have adopted and modified cellular pathways as a means of transforming T and B lymphocytes (Fig. 2).

EBV LMP2A, KSHV K15, and HVS Tip also share a common function in the absence of any sequence homology. All three proteins contain SH2-binding and/or SH3-binding motifs that are capable of interacting with either the Src or Syk family

kinases (Fig. 3). These motifs appear to be involved in the down-regulation of lymphocyte receptor signaling. The impairment of cellular signal transduction pathways by these viral proteins may help to reduce or delay the onset of aberrant lytic replication as a result of cellular proliferation triggered by external signals.

OTHER GROWTH-DEREGULATING GENES OF GAMMAHERPESVIRUSES

Herpesviruses have large genomes containing a wide array of genes. Although the first ORFs in these gammaherpesviruses have oncogenic potential, other viral genes may also play a role in viral transformation. These viral genes can be classified into two groups, those that are homologous to cellular genes and those that are unique to the virus. EBV encodes several unique viral genes, e.g., EBNA-1, EBNA-2, and EBNA-3, which all appear to play a role in viral oncogenesis (15, 80, 81, 87, 89, 110, 118, 134, 136). Another such gene is the KSHV K12 (Kaposin) gene, which has been shown to have transforming ability (97), although its contribution to viral pathogenesis is not yet clear. Furthermore, the K12 gene has been shown to undergo a complex translation program (121).

The second set of potential growth-deregulating genes encoded by these viruses are those that resemble cellular genes. EBV, HVS, KSHV, and RRV all harbor a viral *Bcl-2* gene that has anti-apoptotic activity in cell culture (21, 25, 98, 127, 135; Alexander et al., submitted). While EBV induces expression of IL-6, cyclin D, complement-control protein (CCP), and IL-8 receptor expression (10, 14, 68, 128, 129, 135), the three rhadinoviruses appear to have come prepared with their own viral homologues of cellular genes: v-cyclin, v-CCP, and v-IL-8R (3, 4, 4a, 19, 100, 101, 120). In addition, the rhadinoviruses contain genes encoding a latency-associated nuclear antigen (LANA) and a FLICE-inhibitor protein (v-FLIP) (3, 4, 120, 127). Furthermore, KSHV and RRV encode genes for viral IL-6, interferon regulatory factors (v-IRFs), and viral chemokines (v-MIP-I, -II, and -III) (12, 50, 92, 102, 104, 125–127). Thus, the proteins encoded by genes near the ends of the gammaherpesvirus genomes may act in concert with a number of other virus-encoded protein products to achieve cell growth transformation.

CONCLUSION

Infected hosts induce numerous antiviral responses that include apoptosis, immune activation, and cell growth arrest. The *Gammaherpesvirinae* have evolved means of altering these signal transduction pathways by deregulating expression of a subset of cellular signaling genes or encoding their own viral counterparts to these genes. Thus, acting in concert with other viral genes, STP and Tip of HVS, LMP1 and LMP2a of EBV, K1 and K15 of KSHV, and R1 and R15 of RRV are capable of modulating cellular signals such that cell proliferation and viral replication occur at the appropriate times in the viral life cycle.

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