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Antiviral activity of tumor-suppressor pathways: clues from molecular piracy by KSHV

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A common feature of many tumor viruses is that they possess genes that produce specific proteins to inhibit major cellular tumor-suppressor pathways. Despite intensive studies, the reasons why these diverse and unrelated viruses have independently evolved oncogenes remains obscure. Kaposi-sarcoma-associated herpesvirus (KSHV or HHV8) has pirated a number of recognizable cellular genes that are key to cell survival and proliferation. In this review, we provide an overview of the known activities of these viral genes and show that many of these pirated proteins affect the same cellular pathways targeted by other, unrelated tumor viruses. We speculate that tumor-suppressor pathways are used by the cell as a primary defense against persistent virus infection, in addition to their well-known activity in regulating cell proliferation.

The development of a tumor induced by a virus has several evolutionary disadvantages for the virus and few clear benefits. Cell doubling through tumorigenesis is inefficient for creating progeny viruses compared with active lytic replication, and the formation of a tumor can kill the host. Because tumor viruses generally cause tumors while in a nontransmissible latent stage, tumor-cell proliferation does not increase the virus' opportunity to be transmitted to a new host. Nonetheless, a number of tumor viruses contain oncogenes that inhibit tumor-suppressor pathways specifically and contribute to tumor formation. In this review, we speculate that this apparent paradox becomes understandable if the major cellular tumor-suppressor pathways serve the dual function of also preventing virus replication. Viral oncogenes might inhibit these cellular defenses and, under unusual circumstances, promote the uncontrolled cell proliferation that is characteristic of a tumor. We provide a brief overview of the most recently discovered human tumor virus, Kaposi-sarcoma-associated herpesvirus (KSHV or human herpesvirus 8), and how it contributes to understanding of the general principles of virus-induced tumorigenesis.

Virus-induced tumor formation as a biological accident

There is considerable evidence that tumor formation resulting from infection is generally a biological dead-end for the infecting pathogen. Tumors arising after infection with some parasites and microorganisms, such as schistosomes, *Helicobacter pylori* and perhaps hepatitis C virus, are probably the result of nonspecific, chronic inflammation. In contrast, there are a number of well-characterized tumor viruses that possess specific oncogenes that can directly transform cells in culture or cause tumors in experimental animals. Infection of these tumor viruses' natural hosts, however, does not generally result in tumor formation. Adenoviruses and herpesvirus saimiri, for example, cause tumors only in non-natural hosts[1,2]

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and other virus-associated tumors occur in natural hosts but only under abnormal host or virus conditions. Infection of healthy humans with Epstein–Barr virus (EBV or human herpesvirus 4) rarely causes tumors and requires complementing overexpression of cellular *MYC* for EBV-associated Burkitt's lymphoma, or immunosuppression for other EBV-related lymphoproliferative disorders and leiomyosarcomas[3]. Similarly, papillomavirus-associated anogenital cancers frequently occur after viral genome integration (in which the virus is nontransmissible) and loss of transcriptional control over viral oncogenes. Hepatocellular carcinomas arise among persons with decades-long hepatitis B virus (HBV) infection and are unlikely to contribute significantly to the propagation of HBV in the human population.

TABLE 1. Tumor-suppressor pathway inhibition by selected DNA viruses[a]

Virus	RB1 pathway	p53 (TP53) pathway	Interferon signaling
Adenovirus	E1A	E1B55k,19k and E4	E1A
Papillomavirus	E7	E6	?
SV40	LT	LT	LT[b]
EBV	EBNA2/EBNA-LP	LMP1, BHRF1	Unk[c]
HVS	ORF 72 (vCyc)	ORF 71 (vFLIP)? ORF 16 (vBCL2)?	?
KSHV	ORF 72 (vCyc)	ORF K13 (vFLIP)? ORF K2 (vIL6)? ORF K9 (vIRF)? ORF 16 (vBCL2)?	ORF K9 (vIRF)

[a]Does not include RNA tumor viruses or infectious agents that might act through nonspecific, inflammatory mechanisms.
[b]In large T antigen (LT) transgenic mouse tissues. LT also induced by IFN treatment.
[c]Qp promoter responsive to interferon regulatory factors (IRF) 1, 2 and 7.
Abbreviations: SV40, simian virus 40; EBV, Epstein–Barr virus; HVS, herpesvirus saimiri; KSHV, Kaposi-sarcoma-associated herpesvirus.

The events leading to tumorigenesis are poorly understood for most virus-induced tumors, but for many of these viruses tumor formation is likely to be a biological accident, rather than a central feature of their lifecycles. Nonetheless, several phylogenetically unrelated tumor viruses contain oncogenes that show a remarkable evolutionary convergence in their inhibition of RB1 and p53 (TP53) tumor-suppressor pathways (Table 1). In fact, the discovery of several key regulators of these pathways originated from their interactions with known viral oncoproteins. If the primary purpose of these viral oncogenes is not related to tumorigenesis *per se*, then why are they conserved?

The limited-resource and the cellular-defense hypotheses

One widely held view is that when intracellular resources are limited, viral oncogenes optimize cellular conditions for virus replication. This can be achieved by inhibition of the retinoblastoma tumor-suppressor protein, RB1, which regulates cellular transit across the G1 cell-cycle checkpoint by binding E2F transcriptional factors required for the expression of some DNA-synthesizing enzymes. RB1 inhibition can stimulate a quiescent cell to enter into S phase and express high levels of endogenous enzymes required for virus replication[4,5]. Furthermore, Teodoro and Branton have proposed that some viruses induce apoptosis to enhance virus packaging and transmission[6]. However, prevention of premature apoptosis, for example, via inhibition of the apoptosis-promoting p53 tumor-suppressor protein (reviewed in Ref. 7), is necessary to optimize virus replication. In this scheme, the inhibition of tumor-suppressor pathways is primarily beneficial to lytic virus replication.

A different explanation from the limited-resource hypothesis proposes an active role for tumor-suppressor pathways in preventing virus replication[8–12]. In essence, the 'cellular-defense hypothesis' proposes that cells use tumor suppressors such as RB1 and p53 to control virus infection as well as to prevent dysregulated cell proliferation. Activation of these pathways arrests DNA synthesis and primes the infected cell for destruction through apoptosis. Tumor-cell proliferation and virus replication both involve dysregulated nucleic acid synthesis and the cell could use similar pathways to control both processes. During latency, when virus-antigen expression is minimized, this may be the optimal mechanism for controlling the replication of nonself nucleic acid. Viral oncogenes that inhibit these cellular antiviral defenses would favor a transformed phenotype[13]. The limited-resource and the cellular-defense hypotheses are not mutually exclusive, and it is possible that viral oncogenes optimize cellular resources during lytic replication and prevent tumor-suppressor pathway activation during latent replication.

KSHV

KSHV provides an important comparative model for investigating virus–host cell interactions. Other DNA tumor viruses have evolved multifunctional oncogenes with little or no sequence similarity to known cellular genes. KSHV, however, has evolved through genetic piracy to possess homologs to a number of recognizable cellular regulatory genes. While studies on KSHV are still at an early stage, examination of these KSHV homologs and the cellular pathways that they modify provides important clues about viral tumorigenesis.

KSHV was discovered by representational difference analysis in the search for the 'KS agent'[14]. Subsequent studies demonstrate that KSHV largely fulfills Hill's criteria for KS causation and KSHV infection is a necessary precondition for nearly all KS tumors (for review, see Ref. 15). The virus is also present in body cavity-based lymphomas[16], a rare non-Hodgkin B cell lymphoma frequently co-infected with EBV, and some forms of Castleman disease[17], a hyperplastic lymphoproliferative disorder associated with IL6 overexpression.

KSHV is a large-genome herpesvirus (approximately 165 kb), belonging to the genus *Rhadinovirus* and encoding conserved structural and DNA-replication proteins that are characteristic for members of the herpesvirus family (Fig. 1). Its genomic structure is most similar to closely

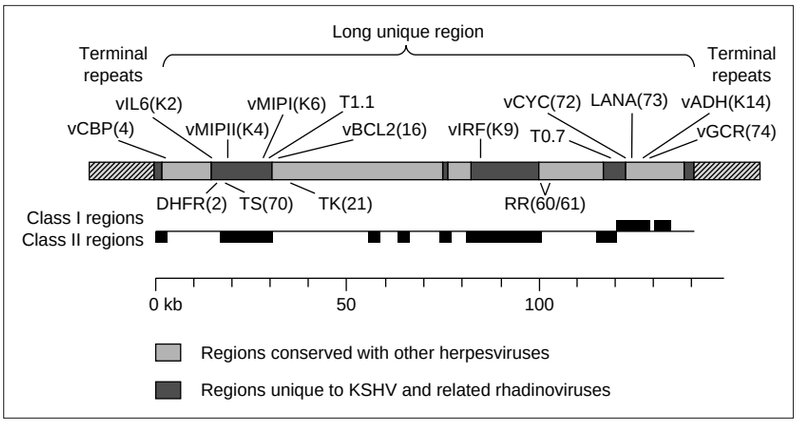

FIGURE 1. The Kaposi-sarcoma-associated herpesvirus (KSHV or HHV8) genome can be divided into regions that are highly conserved with all subfamilies of herpesviruses (pale grey), and intervening regions that are only found in KSHV or in other closely related rhadinoviruses (dark grey). The genes that are homologous to cell regulatory genes (described in the text) are clustered in the nonconserved regions of the genome, shown here with open reading frame (ORF) designations in parentheses. Beneath the genome map, regions containing class I and class II genes expressed during latency in body cavity-based lymphoma cells are shown. The class II genes are expressed at low levels during latency but these expression levels increase during lytic replication, whereas the class I transcription levels are similar during both latent and lytic virus replication. Class I and II latency genes also cluster within the nonconserved regions. KSHV and herpesvirus saimiri encode a more extensive array of DNA-synthesis enzymes than other human herpesviruses, including a dihydrofolate reductase (DHFR), thymidylate synthase (TS), a thymidine kinase (TK) and a ribonucleotide reductase (RR). The cellular versions of these enzymes are under E2F transcriptional control[68], regulated by the RB1 tumor-suppressor protein. Expression of the viral enzymes might allow KSHV replication even under conditions where RB1 is activated (i.e. outside of the S phase of the cell cycle).

related lymphotrophic gammaherpesviruses, such as EBV and herpesvirus saimiri (HVS or saimariine herpesvirus 2), which are well-characterized tumor viruses[18]. However, KSHV does not possess genes that are related to the EBNA/LMP or STP/TIP oncogenes known to be important for *in vitro* immortalization by EBV and HVS, respectively. KSHV currently cannot be transmitted *in vitro* to any significant degree and, therefore, analysis of genomic deletion mutants is not feasible. To identify potential KSHV oncogenes, several laboratories have examined isolated genes and genomic regions. A major caveat to current KSHV transformation studies is that these genes are examined in isolation and the results must be interpreted cautiously.

Piracy of cellular regulatory genes by KSHV

The KSHV genome displays an unusual degree of genetic piracy compared with other herpesviruses[19] (Fig. 1). Between blocks of conserved herpesvirus genes lie genes that are unique to KSHV, or genes that are found only in closely related gammaherpesviruses[18]. KSHV genes are named after corresponding genes from the prototypic *Rhadinovirus*, HVS (ORFs 4–75), or are given a 'K' prefix (ORFs K1–15) if they are unique to KSHV. Pirated genes include: a complement receptor-like protein (ORF 4); three macrophage inflammatory protein (MIP)-like chemokines (ORFs K4, K4.5 and K6); an IL6-like cytokine (ORF K2); a BCL2-like protein (ORF 16); an interferon regulatory factor (IRF)-like signal-transduction protein (ORF K9); an antiapoptotic FLICE-inhibitory protein (ORF K13); a cyclin (ORF 72); an IL8 receptor-like protein (ORF 74); and a homolog to the rat OX2 adhesion molecule (ORF K14). Mapping studies show that the transcriptional activity of the virus tends to cluster to these nonconserved regions during latency in lymphoma cells, and that these latency-expressed genes can be classified into those that are (class II genes) or are not (class I genes) further induced by lytic virus replication[20,21]. The cellular counterparts for many of these KSHV genes are induced by EBV infection, suggesting that both lymphotrophic viruses affect similar cell regulatory pathways[10,18] (see Table 2). The TAX oncoprotein of the human T cell lymphotrophic virus I (HTLV I) also induces the expression of cellular IL6, β-chemokines and an IRF transcriptional repressor (IRF4)[22–24], which have functionally similar representatives in the KSHV genome.

Table 2. Correspondence between KSHV and EBV regulatory genes

KSHV Genes	Effect	Cell protein induced by EBV	Responsible EBV proteins	Refs
ORF 4 (vCBP)	Complement inactivation?	Cd21/CR2	EBNA2	69
ORF K2 (vIL6)	Growth factor	IL6	gp350/220 and LMP1	70, 71
ORFs K4/6 (vMIPII/I)	β-chemokines	MIP-1α,β, RANTES	EBV induced	a
ORF 16 (vBCL2)	Anti-apoptosis	BCL2	LMP1 and BHRF-1	35, 39, 72
ORF K9 (vIRF)	Inhibition of interferon	?	EBNA2 and BCRF1	53, 73
ORF 72 (vCYC)	Cell-cycle control	Cyclin D2	EBNA-2 and EBNA-LP	29
ORF 74 (vGCR)	Cellular proliferation?	EBI1	EBV induced	63

[a]G. Tosato, pers. commun.
KSHV and EBV (both are gammaherpesviruses that infect B lymphocytes) modify similar intracellular regulatory pathways, but do so through separate mechanisms: KSHV has incorporated modified eukaryote genes into its genome while EBV induces cellular gene expression. Table lists some of the pirated KSHV genes and their cellular counterparts induced by specific EBV proteins.

Potential KSHV-encoded oncogenes

Candidate KSHV oncogenes have been identified by their sequence homology, and *in vitro* experiments demonstrate their potential to promote cell proliferation and, in some cases, transformation. The first gene studied actively was the KSHV cyclin (ORF 72), which is expressed as a class I gene during virus latency and is most similar to D-type cyclins. D-type cyclins act in the G1 phase of the cell cycle by associating with cyclin-dependent kinases (CDKs) to phosphorylate and inactivate RB1, allowing entry into S phase (reviewed in Ref. 25). Functional studies demonstrate that vCYC can complex with CDK6 and induce cell proliferation when co-transfected with wild-type RB1 (Refs 26–28). Unlike cellular D cyclins, vCYC can also direct the phosphorylation of histone H1.

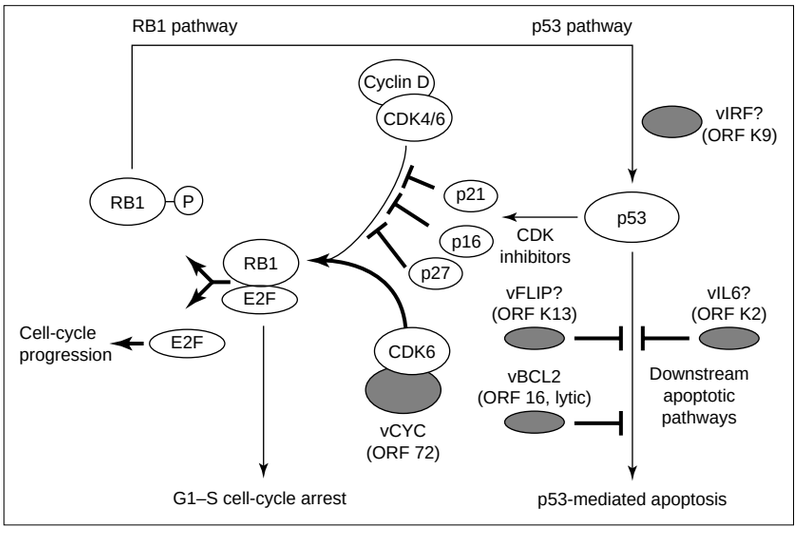

FIGURE 2. The potential interrelationship between pirated KSHV genes and cellular tumor-suppressor pathways is shown in this simplified schematic diagram. The tumor-suppressor protein RB1 controls the entry of the cell into S phase of the cell cycle by binding to E2F transcriptional factors, preventing the transcription of factors and enzymes required for DNA synthesis. Inhibition of this checkpoint by RB1 mutations or viral oncogenes results in p53 (TP53) activation, which can lead to shutdown of the cell cycle through p21 (CDKN1A) induction or apoptosis. The KSHV vCYC might override these controls by phosphorylating and inactivating RB1. The viral cyclin is not responsive to cellular cyclin-dependent kinase inhibitors [p16 (CDKN2A), p21, p27, Ref. 32], which inactivate human cyclins normally controlling RB1 activity. The KSHV genome also encodes a number of proteins (vIRF, vBCL2, vIL6, vFLIP) that might prevent p53-mediated apoptosis activation after RB1 inhibition, although this has not yet been demonstrated directly. The vIRF inhibits interferon activation of tumor-suppressor pathways and might help the virus evade immune responses.

The conserved requirement of many tumor viruses to inhibit RB1 is striking (Table 1). Adenoviruses, papillomaviruses and SV40 encode E1A, E7 and LT oncoproteins, respectively, which inhibit RB1. Similarly, the EBV EBNA2/EBNA-LP and HTLV I TAX oncoproteins indirectly inhibit RB1, either by inducing cellular cyclins[29] or inhibiting the CDK inhibitor, p16 (CDKN2A) (Refs 30, 31). The latent expression pattern for vCYC strongly argues for the requirement of RB1-inhibition for KSHV latency, in contrast with the limited-resource hypothesis. Unlike cellular D-type cyclins, vCYC is not inactivated by the cellular CDK inhibitors p16, p21 (CDKN1A) and p27 (Ref. 32), which might allow KSHV to override cell growth control signals.

Is there evidence that tumor-suppressor pathways act in intracellular defense against virus infection? Inappropriate RB1 inhibition activates p53, which, in turn, either re-establishes control of the cell cycle through the induction of p21 CDK inhibitor, or initiates apoptotic cell death[33] (Fig. 2). RB1 and p53 must both be inactivated simultaneously for some tumor viruses to infect cells successfully. Adenoviruses, which express the RB1-inhibiting *E1A* oncogene but lack the *E1B* oncogene that inhibits p53, for example, are only capable of replicating in tumor cells that have p53 mutations[34]. A similar short-circuiting of RB1 control pathways by KSHV vCYC could be expected to lead to p53-dependent proliferation arrest or apoptosis; experimental evidence indicates that stable overexpression of vCYC in NIH3T3 cells is not achievable, because cells die or fail to proliferate (C. Boshoff and R. Sarid, unpublished).

Currently, no direct evidence exists for other KSHV genes that inhibit p53 activity, but KSHV encodes several possible candidates that can prevent apoptosis[18]. KSHV, like EBV and HVS (Refs 35, 36), encodes a protein (ORF 16) with sequence similarity to the BCL2 family of apoptosis inhibitors (reviewed in Ref. 9) that inhibits BAX-mediated cell death[37,38]. These herpesvirus BCL2 homologs, however, are primarily active during lytic replication. During latency, EBV LMP1 induces cellular *BCL2* (Ref. 39) and *BCL2* expression is also increased in KS lesions[40,41]. It remains to be seen whether a KSHV protein, analogous to the EBV LMP1, directly induces cellular *BCL2* expression, which may then inhibit p53-activated apoptosis.

Another potential antiapoptotic factor encoded by KSHV is vIL6 (ORF K2), which is expressed in cell culture at lower levels during latency and is induced to higher levels during lytic replication (class II expression)[10]. vIL6 is not expressed significantly in KS lesions but is secreted by KSHV-infected hematopoeitic cells. Similar to endogenous IL6, vIL6 signals via STAT1 and STAT3, preventing apoptosis in the IL6-dependent mouse myeloma cell line B9 (Refs 10, 42, 43). It differs from endogenous IL6 in that it appears to be able to activate the GP130 receptor protein directly in the absence of the IL6Rα co-receptor and, thus, could have a broader cellular activity than the human cytokine[42]. IL6 is an autocrine factor induced by EBV infection and enhances the tumorigenicity of EBV-infected lymphoblastoid cell lines[44]. HVS TIP oncoprotein constitutively activates T cell STAT1 and STAT3 (Ref. 45), although it is not clear that this is functionally equivalent to IL6 signaling. Expression of vIL6 in KSHV-infected Castleman disease lesions (Fig. 3) is probably responsible for the lymphoproliferation that characterizes the KSHV-related variant of this disorder[46].

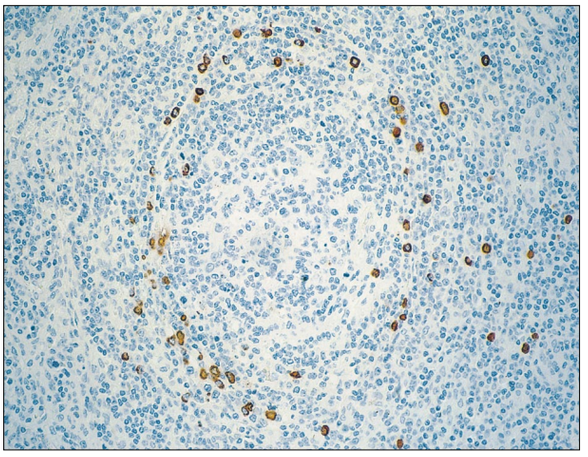

FIGURE 3. Castleman disease is a non-neoplastic lymphadenopathy-associated B cell expansion. Approximately half of Castleman disease samples are infected with KSHV, in which the viral cytokine vIL6 is expressed (brown staining). vIL6 might induce cell proliferation by either inhibiting the normal rate of apoptotic B cell death or by promoting B cell proliferation[46]. (Image kindly provided by C. Parravicini.)

An additional KSHV protein with potential anti-apoptotic activity is encoded by ORF K13 (vFLIP, viral FLICE inhibitory protein) and belongs to a recently recognized class of dominant negative inhibitors of the FAS/APO1-activated apoptosis pathway[47,48]. No functional studies have been performed on KSHV vFLIP; however, the HVS homolog to vFLIP can inhibit FLICE (caspase-8)-mediated apoptosis. KSHV vFLIP is expressed together with vCYC on the polycistronic LT1 and LT2 transcripts during latency[21]. While it is attractive to speculate that these or other yet to be described KSHV-encoded proteins may also inhibit p53-dependent apoptosis resulting from vCYC expression, experimental studies are still ongoing.

The interferon connection

Examination of the KSHV genome also highlights an important but little-studied relationship of tumor viruses with inhibition of interferon (IFN) signaling[49]. The KSHV ORF K9 (vIRF) protein[10] is related to members of the interferon regulatory factor (IRF) transactivator family involved in IFN-mediated transcription (Fig. 4, reviewed in Ref. 50). IRF proteins generally possess both an N-terminus DNA-binding motif that recognizes specific promoter elements and a C-terminus transcription activator/repressor motif. Three additional KSHV sequences that are similar to IRF genes are also present in the genome but have not been shown to be functional genes[18].

When IFN interacts with its receptor, gene expression is induced through JAK–TYK activation of specific transcriptional factors which in turn bind to promoters of the IFN-inducible genes. For class I IFN signaling, the primary transcriptional factor activated by IFN is ISGF3, which is a trimeric complex of phosphorylated STAT1, STAT2 and ISGF3γ (or p48). The ISGF3 complex translocates to the nucleus and binds to specific recognition sequences (IFN-stimulated response elements) in inducible promoters. Activation of genes possessing these IFN-responsive elements results in characteristic IFN-induced cellular changes, such as expression of major histocompatibility complex (MHC) antigens, cell cycle shut-down through p21 expression, and priming of apoptotic pathways.

Secondary transcription factors belonging to the IRF family are also induced by IFN signaling, and these factors can either amplify or antagonize the IFN response by competitively binding to IFN-responsive promoter elements. IFN-γ treatment, for example, induces IRF1 which, in turn, induces transcription of IFN-inducible genes, forming a positive feedback loop to rapidly enhance and broaden the IFN response[50]. This is antagonized by a second transcriptional repressor, IRF2, also induced by IFNs but having a longer half-life than IRF1, which competes with IRF1 and ISGF3 at promoter elements to turn off the IFN response.

Gao *et al.*[51] and Zimring *et al.*[52] have shown that vIRF effectively inhibits IFN signaling, as measured by reporter assays, suggesting a novel mechanism for KSHV to escape host immune responses. While vIRF functionally resembles IRF2, it does not bind IFN-responsive promoter elements directly, nor does it complex with IRF1 or IRF2 (Refs 51, 52). Adenovirus oncoproteins E1A (Ref. 8) and EBV EBNA2 (Ref. 53) also inhibit IFN responses, indicating that this could be a common feature for some tumor viruses, and the expression patterns of EBV latency genes have recently been found to be regulated in part by host-cell IFN signaling.

Interferon signaling, however, also activates a number of cellular pathways that are less clearly linked to cell-mediated immune responses. IFN-response pathway activation initiates cell cycle arrest and primes the cell towards apoptosis through p53-dependent and -independent pathways[54]. This is probably achieved through IRF1 induction of cyclin-dependent kinase inhibitors such as p21 (Refs 55, 56), as well as other factors, such as the transcriptional repressor p202 (Ref. 57). The advantage to the host of linking IFN signaling to tumor-suppressor pathways is that IFN can shut off nucleic acid synthesis in uninfected cells, preventing nascent infections, and drive infected cells into apoptosis, which limits virus spreading. Induction of MHC molecules by IFN also enhances the ability of the immune system to detect infected cells in which latent viruses are expressing a minimized set of antigens.

The close interrelationship between IFN activation and tumor-suppressor pathways suggests that inhibition of IFN signaling could contribute to neoplasia. This connection was clearly demonstrated by Harada *et al.*[58], who showed that overexpression of IRF2 is oncogenic in NIH3T3 cells and this effect can be reversed by IRF1 coexpression. Similar to IRF2, KSHV vIRF prevents IFN induction of p21 and fully transforms NIH3T3 cells[51].

Thus, positive IFN signaling in response to virus infection sets in motion a cellular program that is similar to that used to control tumor proliferation. The practical consequences of this have long been recognized by the clinical utility of IFNs as antitumor drugs. Inhibition of IFN signaling may be a third common feature of tumor viruses, although this picture is far from complete (Table 1). Viral strategies to overcome IFN-mediated antiviral activity are likely to substantially contribute to transforming the host cell.

Other cellular signaling pathways

KSHV also encodes two membrane-bound proteins, ORF K1 and vGCR (ORF74), which may activate cellular signaling pathways involved in mitogenesis. ORF K1 encodes a transmembrane protein in a region of the KSHV genome, corresponding to the HVS TIP/STP oncogenes, that has no homology to other known cellular or viral proteins[59]. The vGCR is a seven transmembrane-spanning G-protein coupled receptor (GCR), with homology to a number of cellular GCRs including the IL8 receptor involved in neoangiogenesis[60]. NIH3T3 cells are transformed by vGCR expression[61] and this constitutively active receptor[62] induces the expression of vascular endothelial cell growth factor, pointing towards a unique potential mechanism for the neoangiogenesis associated with KSHV-related tumors[61]. HVS also encodes an IL8-like receptor homolog (HVS ECRF3) and EBV upregulates expression of a cellular GCR, EBI1 (Ref. 63). In addition, KSHV encodes two viral chemokines, vMIP-I and vMIP-II, that inhibit HIV infection by competition with chemokine co-receptors[10,64,65] and also induce neoangiogenesis in chicken chorioallantoic membrane assays[65]. A third chemokine-like gene is present in the KSHV genome that is distinct from known classes of chemokines and has not been functionally evaluated. The role of these signaling molecules in KSHV-related angiogenic proliferation, especially KS and Castleman disease, remains to be explored.

KSHV: a Rosetta stone fragment?

Although KSHV is present in virtually all tumor cells of mature KS lesions, it remains hotly debated whether KS lesions are virus-driven clonal cell expansions, polyclonal disorders similar to EBV-associated lymphoproliferative disease, or non-neoplastic cytokine-induced hyperplasias. This is not the case for body cavity-based lymphomas in that cells and virus from this tumor are monoclonal[16,18]. Thus, KSHV is probably a directly transforming tumor virus, although this activity might be more applicable to body cavity-based lymphomas than KS lesions.

KSHV presents a readily accessible model for tumor virus–host cell interactions despite serious limitations in the ability to cultivate it *in vitro*. Although KSHV research is in its infancy, this virus lends itself to deciphering the mechanisms of action for other tumor virus oncogenes as well. The correspondence between KSHV genes and EBV-induced cellular genes suggests avenues for research on regulatory pathways that are modified by tumorigenic herpesviruses. More broadly, the functions of these genes suggest that tumor-suppressor pathways are intimately linked to antiviral defense mechanisms. This also implies the presence of an intracellular sensor for detecting latent viral genomes that is responsible for activating tumor-suppressor pathways after infection.

Only KSHV genes with obvious homologies to cell regulatory genes have been discussed in this review, but the viral genome contains a number of additional unique genes whose functions have yet to be examined. Even among those viral genes with obvious eukaryote homologies, unique functional activities distinguish them from their cellular counterparts. The roles of other latency-expressed genes in tumorigenesis and maintenance of the viral genome, such as LANA, the major latency-associated nuclear antigen (ORF 73, Ref. 66) and the highly expressed, polyadenylated T1.1 and T0.7 RNAs (Ref. 67), remain unknown. Additional insights will be gained by examining host-related factors for KSHV infection, such as immunosuppression or potential tumor-cell mutations in infected cells. As a new model for a human tumor virus, KSHV and its interaction with the host cell promise a substantial contribution to our fundamental understanding of the biology of tumor viruses.

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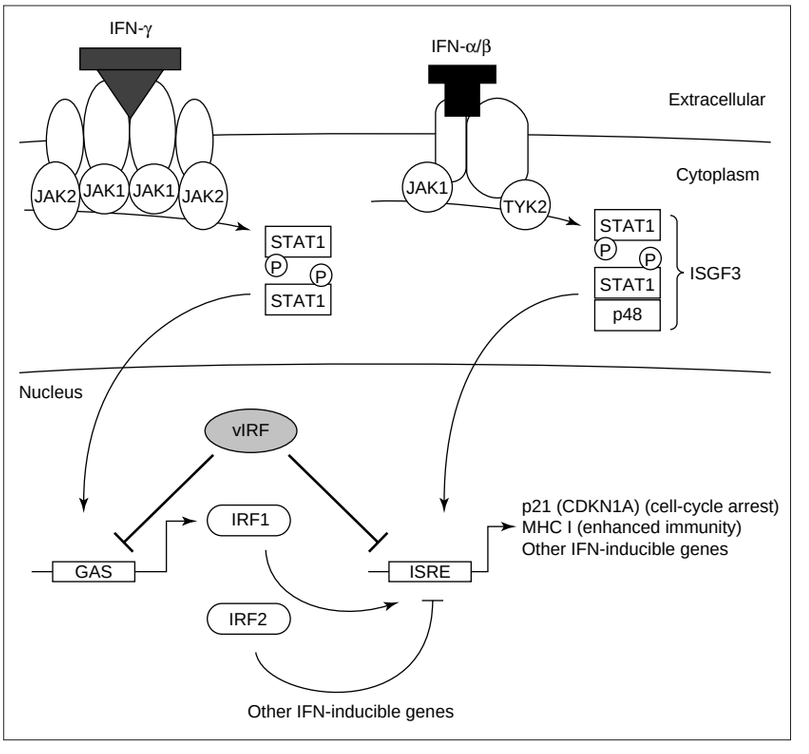

FIGURE 4. Interferon (IFN) signaling through class I (α/β) or class II (γ) activation leads to IFN-inducible gene transcription. Secondary transcriptional activators (e.g. IRF1) or repressors (IRF2) can amplify or inhibit this response. Cellular changes resulting from IFN treatment include inhibition of proliferation, apoptosis and enhanced MHC-antigen expression. Overexpression of IRF2 can lead to cell transformation that is reversible by coexpression of IRF1. Like IRF2, the KSHV vIRF inhibits both class I and class II signaling and transforms cells, but does not compete with or bind to IRF1 or IRF2 directly. More complex cross-signaling mechanisms than those shown here also occur (see Ref. 53).

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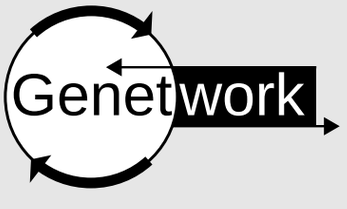

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