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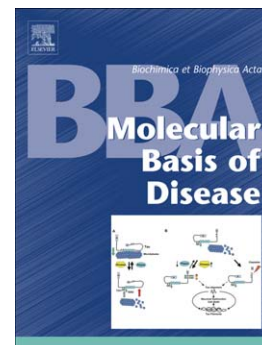
Viruses Associated with Human Cancer

Margaret E. McLaughlin-Drubin, Karl Munger

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1 **Viruses Associated with Human Cancer**

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22  
23 **Keywords:** Human T-Cell Leukemia Virus (HTLV-1), Hepatitis C Virus (HCV), Human  
24 Papillomavirus (HPV), Hepatitis B Virus (HBV), Epstein-Barr Virus (EBV), Kaposi's Sarcoma-  
25 Associated Herpesvirus (KSHV)/Human Herpes Virus 8 (HHV8)

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**1 Abstract**

2           It is estimated that viral infections contribute to 15-20% of all human cancers. As  
3 obligatory intracellular parasites, viruses encode proteins that reprogram host cellular signaling  
4 pathways that control proliferation, differentiation, cell death, genomic integrity, and recognition  
5 by the immune system. These cellular processes are governed by complex and redundant  
6 regulatory networks and are surveyed by sentinel mechanisms that ensure that aberrant cells  
7 are removed from the proliferative pool. Given that the genome size of a virus is highly  
8 restricted to ensure packaging within an infectious structure, viruses must target cellular  
9 regulatory nodes with limited redundancy and need to inactivate surveillance mechanisms that  
10 would normally recognize and extinguish such abnormal cells. In many cases, key proteins in  
11 these same regulatory networks are subject to mutation in non-virally associated diseases and  
12 cancers. Oncogenic viruses have thus served as important experimental models to identify and  
13 molecularly investigate such cellular networks. These include the discovery of oncogenes and  
14 tumor suppressors, identification of regulatory networks that are critical for maintenance of  
15 genomic integrity, and processes that govern immune surveillance.

16

## 1    **1.    Introduction**

2            With 10.9 million new cases and 6.7 million deaths per year, cancer is a devastating  
3 disease, presenting an immense disease burden to affected individuals and their families as  
4 well as health care systems [1]. Development of treatment and prevention strategies to manage  
5 this disease critically depends on our understanding of cancer cells and the mechanism(s)  
6 through which they arise. In general terms, carcinogenesis represents a complex, multi-step  
7 process. During the past 30 years it has become exceedingly apparent that several viruses play  
8 significant roles in the multistage development of human neoplasms; in fact, approximately 15%  
9 to 20% of cancers are associated with viral infections [2, 3]. Oncogenic viruses can contribute  
10 to different steps of the carcinogenic process, and the association of a virus with a given cancer  
11 can be anywhere from 15% to 100% [3]. In addition to elucidating the etiology of several human  
12 cancers, the study of oncogenic viruses has been invaluable to the discovery and analysis of  
13 key cellular pathways that are commonly rendered dysfunctional during carcinogenesis in  
14 general.

## 16    **2.    Historic Context**

17            The belief in the infectious nature of cancer originated in classical times as evidenced by  
18 accounts of “cancer houses” in which many dwellers developed a certain cancer. Observations  
19 that married couples sometimes could be affected by similar cancer types and that cancer  
20 appeared to be transmitted from mother to child lent further support to an infectious etiology of  
21 tumors. However, during the 19<sup>th</sup> century, extensive investigations failed to demonstrate a  
22 carcinogenic role for bacteria, fungi, or parasites leading to the belief that cancer is not caused  
23 by an infectious agent. Despite the prevailing dogma, a small number of researchers  
24 hypothesized that the failure to detect an infectious cause of cancer did not necessarily mean  
25 that the general idea of the infectious nature of cancer was invalid. Rather, they hypothesized

1 that the causal organism had merely not yet been found and that smaller entities not detectable  
2 by standard microscopy may indeed be the culprits. Despite increasing evidence to suggest  
3 that infectious entities of sub-microscopic size may be associated with cancer, acceptance of  
4 this hypothesis took many years. M'Fadyan and Hobday described the cell-free transmission of  
5 oral dog warts with cell free extracts in 1898 [4], and Ciuffo published similar transmission  
6 studies with human warts in 1907 [5]. The significance of these findings was not fully  
7 appreciated since warts are benign hyperplasias and not malignant tumors. In 1908, Ellermann  
8 and Bang demonstrated that leukemia in birds could be transmitted from animal to animal via  
9 extracts of leukemic cells or serum from diseased birds [6]. However, at the time it was not  
10 realized that this was the first successful transmission of a naturally occurring tumor, as  
11 leukemia was not yet accepted as a cancer. In 1911, Peyton Rous produced solid tumors in  
12 chickens using cell-free extracts from a transplantable sarcoma [7]. This study was also met  
13 with considerable skepticism due to the fact that infectious cancers of birds were not considered  
14 valid models for human cancers. In fact, the importance of this study was not fully appreciated  
15 until the finding that murine leukemias could be induced by viruses [8, 9]. Over the next two  
16 decades numerous additional animal oncogenic viruses were isolated, Rous was awarded the  
17 Noble Prize for his pioneering work in 1966, and the importance of the early work on animal  
18 tumor viruses was finally recognized. In fact, the enthusiasm for these findings contributed in no  
19 small part to President Nixon signing the National Cancer Act into law in 1971 and declaring the  
20 "War on Cancer".

21 After the successes of the animal tumor virus field, scientists began the search for  
22 human tumor viruses. However, initial attempts to isolate transmissible carcinogenic viruses  
23 from human tumors proved disappointing, once again raising doubts about the existence of  
24 human cancer viruses. The discovery of Epstein-Barr virus (EBV) by electron microscopy (EM)  
25 in cells cultured from Burkitt's lymphoma (BL) in 1964 [10] and the discovery of hepatitis B virus  
26 (HBV) in human sera positive for hepatitis B surface antigen in 1970 [11], together with the

1 development of animal and cell culture model systems, resulted in a renewed interest in the  
2 roles of viruses in human cancer. The search for additional human tumor viruses continued,  
3 and, despite several setbacks, the ultimate acknowledgment of the causal relationship between  
4 viruses and human cancer occurred during the early 1980s, due in large part to three major  
5 discoveries during that time. In 1983 and 1984, human papillomavirus (HPV) 16 and 18 were  
6 isolated from human cervical cancer specimens [12, 13]. Additionally, although the link between  
7 HBV and liver cancer had been suspected for decades, the results of a large-scale  
8 epidemiological study provided a compelling link between persistent HBV infection and liver  
9 carcinogenesis [14]. The third major discovery was the isolation of the human T-cell leukemia  
10 virus (HTLV-I) from T-cell lymphoma/leukemia patients [15, 16]. Since their initial discovery,  
11 associations of these viruses with cancers at other anatomical sites have been discovered.  
12 Moreover, new links between viruses, most notably hepatitis C virus (HCV) [17] and human  
13 herpes-virus 8 (HHV8)/Kaposi's sarcoma herpesvirus (KSHV) [18], and human cancers have  
14 been discovered. Today, viruses are accepted as bona-fide causes of human cancers, and it  
15 has been estimated that between 15 and 20% of all human cancers may have a viral etiology [2,  
16 3].

### 18 **3. General Aspects of Viral Carcinogenesis**

19 The infectious nature of oncogenic viruses sets them apart from other carcinogenic  
20 agents. As such, a thorough study of both the pathogenesis of viral infection and the host  
21 response is crucial to a full understanding of the resulting cancers. Such an understanding, in  
22 turn, has increased our knowledge of cellular pathways involved in growth and differentiation  
23 and neoplasia as a whole.

24 Even though human oncogenic viruses belong to different virus families and utilize  
25 diverse strategies to contribute to cancer development, they share many common features.  
26 One key feature is their ability to infect, but not kill, their host cell. In contrast to many other

1 viruses that cause disease, oncogenic viruses have the tendency to establish long-term  
2 persistent infections. Consequently, they have evolved strategies for evading the host immune  
3 response, which would otherwise clear the virus during these persistent infections. Despite the  
4 viral etiology of several cancers, it appears that the viruses often may contribute to, but are not  
5 sufficient for, carcinogenesis; in fact, the majority of tumor virus infected individuals do not  
6 develop cancer, and in those patients that do develop cancer many years may pass between  
7 initial infection and tumor appearance. Additional co-factors, such as host immunity and chronic  
8 inflammation, as well as additional host cellular mutations, must therefore also play an important  
9 role in the transformation process. Additionally, there is an obvious geographical distribution of  
10 many virus-associated cancers, which is possibly due to either geographical restriction of the  
11 virus or access to essential cofactors. Thus, the long-term interactions between virus and host  
12 are key features of the oncogenic viruses, as they set the stage for a variety of molecular events  
13 that may contribute to eventual virus-mediated tumorigenesis [19].

14

#### 15 **4. Criteria for Defining an Etiologic Role for Viruses in Cancer**

16 In many cases, viral carcinogenesis is associated with an abortive, non-productive  
17 infection. Hence, the original Koch postulate for the infectious etiology of disease [20] cannot  
18 be applied, as oftentimes no disease causing infectious entity can be isolated from a tumor.  
19 Therefore, it is often difficult to establish a viral cause for a human cancer. As a result, different  
20 guidelines have been proposed to aid in establishing a causal relationship between viruses and  
21 human cancers (Tables 1 and 2) [21-23]. Although some of the guidelines are difficult to meet  
22 and others are not applicable to all viruses, the guidelines are nonetheless quite useful when  
23 evaluating a putative association between a virus and a human malignancy.

24

#### 25 **5. Human Oncogenic Viruses**

1 Human tumor viruses belong to a number of virus families, including the RNA virus  
2 families Retroviridae and Flaviviridae and the DNA virus families Hepadnaviridae,  
3 Herpesviridae, and Papillomaviridae. To date, viruses that are compellingly associated with  
4 human malignancies include; (i) HTLV-1 (adult T-cell leukemia (ATL)) [15], (reviewed in [24]); (ii)  
5 HPV (cervical cancer, skin cancer in patients with epidermodysplasia verruciformis (EV), head  
6 and neck cancers, and other anogenital cancers) [12, 13], (reviewed in [25-28]); (iii) HHV-8  
7 (Kaposi's sarcoma (KS), primary effusion lymphoma, and Castleman's disease) [18], (reviewed  
8 in [29, 30]) (iv) EBV (Burkitt's Lymphoma (BL), nasopharyngeal carcinoma (NPC), post-  
9 transplant lymphomas, and Hodgkin's disease) [10], (reviewed in [31-33]); and (v) HBV and  
10 HCV (hepatocellular carcinoma (HCC)) [11, 17], (reviewed in [34-38]). Viruses with potential  
11 roles in human malignancies include; (i) simian vacuolating virus 40 (SV40) (brain cancer, bone  
12 cancer, and mesothelioma) [39]; (ii) BK virus (BKV) (prostate cancer) [40], (reviewed in [41]); (iii)  
13 JC virus (JCV) (brain cancer) [42], (reviewed in [41]); (iv) human endogenous retroviruses  
14 (HERVs) (germ cell tumors, breast cancer, ovarian cancer, and melanoma) [43, 44]; (v) human  
15 mammary tumor virus (HMTV) (breast cancer) (reviewed in [45]; and (vi) Torque teno virus  
16 (TTV) (gastrointestinal cancer, lung cancer, breast cancer, and myeloma) [46]. General  
17 information about viruses with known and potential associations with human cancer is provided  
18 in Tables 3 and 4, respectively. Studies of the RNA and DNA tumor viruses has led to the  
19 discovery of oncogenes and tumor suppressors and has greatly added to our understanding of  
20 the etiology of carcinogenesis, both virally and non-virally induced.

21

## 22 **5.1. RNA Tumor Viruses**

23 Although retroviruses have been associated with many animal tumors, to date, only one  
24 human retrovirus, HTLV-1, has been associated with human cancers. The biology of HTLV-1  
25 will be discussed in more detail in the next section. Studies with animal retroviruses have been

1 instrumental establishing the concept of oncogenic viruses and led to the discovery of  
2 oncogenes and tumor suppressors as well as other key regulators of cellular signal transduction  
3 pathways. Hence, animal retroviruses warrant some discussion in this review.

4         The advent of modern tumor virology came about with the development of an in vitro  
5 transformation assay for Rous Sarcoma Virus (RSV) [47]. This assay allowed for the genetic  
6 analysis of the retroviral life cycle and retrovirus-induced transformation in cell culture (reviewed  
7 in [48-52]). Retroviruses are classified as either simple or complex viruses based on the  
8 organization of their genomes. Shortly after infection, the viral RNA genome is reverse-  
9 transcribed by the virally encoded reverse transcriptase into a double-stranded DNA copy,  
10 which then integrates into the host chromosome and is expressed under the control of viral  
11 transcriptional regulatory sequences. Once integrated, proviruses are rarely lost from the host  
12 chromosome. As a consequence of integration, and of particular relevance when considering  
13 oncogenesis, is the ability of simple retroviruses to acquire and transduce cellular genetic  
14 material or to activate or inactivate cellular genes via provirus insertion. It was the analysis of  
15 this group, the transducing retroviruses, that led to the finding that the RSV transforming gene,  
16 v-src, hybridized to cellular sequences; ultimately this finding led to the discovery of proto-  
17 oncogenes, a group of cellular genes that mediate viral carcinogenesis and have critical roles in  
18 the control of cell growth and differentiation (reviewed in [48-52]). Since this initial discovery,  
19 numerous animal retroviruses with oncogenic properties have been discovered, and, as is the  
20 case with src, the transduced retroviral oncogenes are derived from cellular sequences and are  
21 not necessary for viral replication [50, 52].

22         The erroneous recombination events that allow for acquisition of host cell derived coding  
23 sequences often leave viral genomes mutated and the virus defective for replication. As such,  
24 these viruses are dependent on replication competent helper viruses to provide the necessary  
25 replication functions in trans. Normal cellular transcriptional and translational controls are lost  
26 once an acquired cellular sequence is incorporated into the viral genome, and the over-

1 expression of a proto-oncogene under the control of strong viral promoters can cause malignant  
2 transformation. Moreover, since the acquired proto-oncogene is not necessary for viral  
3 replication but is replicated through the same error prone mechanisms as the viral genome,  
4 retrovirally acquired proto-oncogenes are subject to frequent mutation and some “activating”  
5 proto-oncogene mutations endow the infected cell with a growth advantage and hence are  
6 selected for over time. Such oncogene transducing retroviruses efficiently transform cells in  
7 culture and cause tumors in experimental animals with very short latency periods. However,  
8 this mechanism is relatively rarely seen in animals in the wild and has not been documented in  
9 humans. Nonetheless, this ‘oncogene piracy’ has proven to be quite useful in laboratory studies  
10 of the actions of oncogenes in cancer. Most remarkably, mutations in cellular oncogenes that  
11 arise in human tumors as a consequence of mutagenic insults are often similar or identical to  
12 those discovered in transducing carcinogenic retroviruses [53].

13 A second group, the cis-acting retroviruses, does not contain host cell derived  
14 sequences but transforms cells by integrating in the vicinity of a cellular proto-oncogene or  
15 tumor suppressor. Unlike the transducing retroviruses, the cis-acting retroviruses retain all of  
16 their viral genes and thus can replicate without the aid of a helper virus. Cis-acting retroviruses  
17 cause malignancy in only a percentage of infected animals after a longer latency period than  
18 that required for transducing retroviruses, and they generally do not efficiently transform cells in  
19 culture. Insertional mutagenesis is a common mechanism observed for rodent, feline, and avian  
20 retroviruses, such as avian leukosis virus and mouse mammary tumor virus (MMTV). Whereas  
21 there is no compelling evidence that such a mechanism significantly contributes to human  
22 carcinogenesis, cloning of affected genes led to the discovery of numerous oncogenes, such as  
23 int-1 [54, 55], int-2 [55], Pim-1 [56], bmi-1 [57], Tpl-1 [58], and Tpl-2 [59], that importantly  
24 contribute to the development of human neoplasms. Moreover, the finding that the Friend  
25 murine leukemia virus had integrated into both alleles of the p53 gene in an erythroleukemic cell

1 line provided critical evidence that p53 was a tumor suppressor rather than an oncogene as was  
2 originally suspected [60].

3

#### 4 **5.1.1. Human T-Cell Leukemia Virus (HTLV-1)**

5 Of more significance to human carcinogenesis, the third mechanism of retroviral  
6 oncogenesis does not involve transmission of a mutated version of a cellular proto-oncogene or  
7 dysregulated expression of proto-oncogenes or tumor suppressor genes near or at the  
8 integration site. The latency period between the initial infection and development of a neoplasm  
9 with this group of viruses is often in the range of several years to several decades. The best-  
10 studied example of these viruses is HTLV-1, the first human retrovirus to be discovered that is  
11 clearly associated with a human malignancy [15, 16]. HTLV-1 is delta-type complex retrovirus  
12 and is the etiologic agent of ATL and tropical spastic paraparesis/HTLV-1-associated  
13 myelopathy (TSP/HAM). HTLV-1 is endemic to Japan, South America, Africa, and the  
14 Caribbean [61, 62]. While it is estimated that approximately 20 million people worldwide are  
15 infected with HTLV-1 [63], only a small percentage (2-6%) will develop ATL [64]. The long  
16 clinical latency, together with the relatively low cumulative lifetime risk of a carrier developing  
17 ATL, indicates that HTLV-1 infection is not sufficient to elicit T-cell transformation. While the  
18 exact cellular events remain unclear, a variety of steps, including virus, host cell, and immune  
19 factors, are implicated in the leukemogenesis of ATL [65] (Figure 1).

20 A number of studies indicate that the multifunctional viral accessory protein Tax is the  
21 major transforming protein of HTLV-1 [66-73]. Tax modulates expression of viral genes through  
22 the viral long terminal repeats (LTRs), and also dysregulates multiple cellular transcriptional  
23 signaling pathways including nuclear factor kappa B (NF- $\kappa$ B) [74-85], serum responsive factor  
24 (SRF) [86-90], cyclic AMP response element-binding protein (CREB) [91-94], and activator  
25 protein 1 (AP-1) [95, 96]. Rather than binding to promoter or enhancer sequences directly, Tax

1 interacts with cellular transcriptional co-activators such as p300/CBP [94, 97-104], and P/CAF  
2 [105]. In addition to its role in transcriptional regulation, Tax is also able to functionally  
3 inactivate p53 [106, 107], p16<sup>INK4A</sup> [108, 109], and the mitotic checkpoint protein, Mitotic Arrest  
4 Deficient (MAD) 1 [110-112]. Additionally, the C-terminal PDZ domain-binding motif of Tax,  
5 which interacts with the tumor suppressor hDLG [113], is important for transformation of rat  
6 fibroblasts [114] and inducing interleukin-2-independent growth of mouse T-cells [115].

7 Unlike other well-established DNA tumor viruses, which generally require continuous  
8 expression of viral oncoproteins to sustain transformation (reviewed in [116]), tax transcripts are  
9 detected in only 40% of ATLs [117], suggesting that Tax may be needed to initiate  
10 transformation, but may not be necessary for maintenance of the transformed phenotype. Tax  
11 is the main target of the host's cytotoxic T lymphocyte (CTL) response; therefore, the repression  
12 of Tax expression allows infected host cells to evade immunesurveillance and allows for the  
13 preferential selection of these cells during the progression of ATL [117]. There are several  
14 mechanisms by which ATL cells lose Tax expression, including the loss of the viral promoter for  
15 tax transcription, the 5'-LTR [117], mutation of the tax gene [118], and epigenetic changes in the  
16 5'-LTR [119, 120].

17 Tax has also been implicated in inducing genomic instability, most prominently  
18 aneuploidy, which, as is the case in many cancers, is a hallmark of ATL [112]. Recent studies  
19 have shown that HTLV-1 Tax expression causes multipolar mitoses, from which aneuploidy can  
20 arise, in two ways [121-123]. First, Tax targets the cellular TAX1BP2 protein, which normally  
21 blocks centriole replication, thus causing numerical centrosome aberrations [121]. Second, it  
22 has been proposed that Tax engages RANBP1 during mitosis and fragments spindle poles,  
23 thereby provoking multipolar, asymmetrical chromosome segregation. Together, these  
24 mechanisms help explain the long-standing observations of aneuploidy and multipolar spindles  
25 in ATL cells ("flower cells") [124]. In addition, several ATL cell lines have been demonstrated to  
26 lack an intact mitotic spindle assembly checkpoint [112], which may be related to binding to

1 MAD1 [110, 111]. Evidence that Tax may act as a mitotic mutator gene, greatly increasing the  
2 incidence of mitotic abnormalities, is consistent with reports that Tax binds to and activates the  
3 anaphase-promoting complex/cyclosome (APC/C), thereby promoting premature securin  
4 degradation and mitotic exit, thus contributing to aneuploidy [125-127]. However, this concept is  
5 not fully accepted as a recent study found that Tax did not increase securin degradation [128].

6 As mentioned previously, alterations of the 5'-LTR, such as deletions or  
7 hypermethylation, are common in ATL cells. As a result, the transcription of viral genes  
8 encoded on the plus strand is often repressed. On the other hand, the 3'-LTR is conserved and  
9 hypomethylated in all ATLs [120]. The HBZ mRNA is transcribed from the 3'-LTR [129, 130]  
10 and is expressed in all ATL cells [131]. Suppression of HBZ gene transcription inhibits the  
11 proliferation of ATL cells; additionally HBZ gene expression promotes the proliferation of a  
12 human T-cell line [131]. It appears that HBZ may have a bimodal function at the mRNA and  
13 protein levels, as the RNA form of HBZ supports T cell proliferation through regulation of the  
14 E2F1 pathway, whereas HBZ protein suppresses Tax-mediated viral transcription through the  
15 5'-LTR [129].

16

### 17 **5.1.2. Hepatitis C Virus (HCV)**

18 HCV is the etiologic agent of posttransfusion and sporadic non-A, non-B hepatitis [17]  
19 and infects approximately 2% of the population worldwide, although the prevalence of HCV  
20 infection varies by geographical location [132]. Persistent infection with HCV is associated with  
21 hepatitis, hepatic steatosis, cirrhosis, and hepatocellular carcinoma (HCC) [133-137]. HCV is a  
22 single stranded RNA virus of the Hepacivirus genus in the Flaviviridae family and is the only  
23 positive-stranded RNA virus among the human oncogenic viruses. Its approximately 9.6 kb  
24 genome contains an open reading frame (ORF) that codes for a 3000 amino acid residue  
25 polyprotein precursor [17] that is cleaved by cellular and viral proteases into three structural

1 proteins (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4a, NS4B, NS5A,  
2 and NS5B) [138].

3 In the vast majority of infected individuals, HCV establishes a persistent and life-long  
4 infection via highly effective viral immune evasion strategies [139-143]. The formation of double  
5 stranded RNA (dsRNA) intermediates during HCV genome replication induces cellular dsRNA-  
6 sensing machinery, which in turn leads to the activation of proteins involved in antiviral  
7 response, including interferons (IFNs), interferon regulatory factors (IRFs), signal transducers  
8 and activators of transcription (STATs), interferon stimulated genes (ISGs) and NF- $\kappa$ B [144].  
9 The HCV core, E2, NS3, and NS5A proteins counteract this cellular response through a variety  
10 of mechanisms, including NS5A and E2 mediated suppression of dsRNA-activated kinase PKR  
11 [139, 142]. HCV is also very effective in subverting T-cell mediated adaptive immunity [140,  
12 141]. Although the underlying mechanisms are still unclear, it is believed that the persistence of  
13 HCV infection is due in part to the selection of quasispecies that have escaped the host immune  
14 response [139].

15 Infection with HCV causes active inflammation and fibrosis, which can progress to  
16 cirrhosis and ultimately lead to tumor development. Numerous co-factors for the development  
17 of HCV-associated HCC exist, including co-infection with HBV and excessive alcohol  
18 consumption [145]. While it is currently thought that chronic inflammation and cirrhosis play key  
19 roles in HCV-induced carcinogenesis, the exact underlying mechanisms are not fully understood  
20 [146]. Moreover, the multiple functions of HCV proteins and their impact on cell signaling have  
21 led to the idea that both viral and host factors also play a role in HCC. Core, NS3, NS4B, and  
22 NS5A have each been shown to be transforming in murine fibroblasts [147] and transgenic mice  
23 expressing HCV core protein develop HCC [148, 149]. In addition, HCV proteins have also  
24 been reported to activate cellular oncoproteins and inactivate tumor suppressors, such as p53  
25 [150], CREB2/LZIP [151], and the retinoblastoma protein (pRB) [152]. Finally, HCV causes

1 genome instability, suggesting that certain HCV proteins may have a mutator function [153]. A  
2 summary of the role of HCV in hepatocellular carcinogenesis is depicted on Figure 2.

3

## 4 **5.2. DNA Tumor Viruses**

5 The human DNA tumor viruses are a diverse group with varied structures, genome  
6 organizations, and replication strategies. Certain DNA tumor viruses, such as HPV, EBV, HBV,  
7 and KSHV, cause malignancies in their natural hosts, whereas other DNA tumor viruses, such  
8 as human adenoviruses, can transform cultured cells and only cause tumors in heterologous  
9 animal models. Unlike oncogenes encoded by animal retroviruses, DNA tumor virus oncogenes  
10 are of viral, not cellular, origin and are necessary for replication of the virus (reviewed in [154]).  
11 In addition to elucidating the etiology of several human diseases, analysis of the DNA tumor  
12 virus oncoproteins has revealed mechanisms controlling mammalian cell growth, ultimately  
13 leading to the discovery of cellular tumor suppressor genes.

14 Studies on the small DNA tumor viruses, which include the adenoviruses,  
15 polyomaviruses, and papillomaviruses, have been instrumental in elucidating the underlying  
16 molecular mechanisms of virus-induced cell transformation. Although these viruses are  
17 evolutionarily distinct, the striking similarities in their transforming functions emphasize the  
18 mutual need of these viruses to utilize the host cell's replication machinery for efficient viral  
19 replication. Much of the understanding of the actions of the small DNA tumor virus oncoproteins  
20 has been derived from the study of the physical associations of the viral oncoproteins with a  
21 variety of cellular tumor suppressors, most notably the associations of adenovirus E1A (Ad  
22 E1A), SV40 large T antigen (TAg) and HPV E7 with the pRB family and adenovirus E1B (Ad  
23 E1B), SV40 TAg, and HPV E6 with p53 (reviewed in [27, 155, 156]).

24 The first major cellular tumor suppressor that was found to be targeted by small DNA  
25 tumor virus oncoproteins is pRB, which was identified as the 105 kDa protein associated with  
26 Ad E1A in adenovirus-transformed cells [157, 158], and has subsequently been identified as a

1 cellular target for SV40 Tag [159] and HPV16 E7 [160]. The binding of Ad E1A, SV40 TAg, or  
2 HPV E7 to pRB results in the disruption or alteration of cellular complexes that normally contain  
3 pRB, resulting in inactivation of growth regulatory functions [161-164]. Cells expressing E1A,  
4 SV40 TAg, or HPV E7 display increased levels of free E2F with associated loss of cell-cycle  
5 dependent regulation of E2F responsive genes [165, 166]. E2F responsive genes play key  
6 roles in cell cycle progression, and thus the association of small DNA tumor virus oncoproteins  
7 with pRB ultimately results in S-phase induction, an essential aspect of these viruses' life  
8 cycles. Despite the fact that the core pRB binding sites of SV40 TAg, HPV E7, and Ad E1A are  
9 similar, the functional consequences of viral oncoprotein association are different. Whereas Ad  
10 E1A inactivates pRB by binding both hypo- and hyper- phosphorylated forms [163], SV40 TAg  
11 specifically interacts with G1-specific, growth suppressive hypophosphorylated form [167] and  
12 HPV16 E7 preferentially binds hypophosphorylated pRB [168, 169] and targets pRB for  
13 proteasome mediated degradation [170-172]. The second major cellular tumor suppressor that  
14 is targeted by small DNA tumor virus oncoproteins is p53, which was originally detected as a  
15 cellular protein complexed with SV40 TAg in SV40-transformed cells [173, 174], and has since  
16 been shown to also complex with high-risk HPV E6 and Ad E1B [175, 176]. The p53 protein was  
17 initially classified as an oncogene because it was cloned from a cancer cell line and contained a  
18 point mutation, and it was only later discovered that the wild type form has tumor suppressor  
19 activity [177, 178].

20 The interaction between SV40 TAg, HPV E6, and Ad E1B with p53 results in the  
21 inhibition of p53's tumor suppressor activities [179-181]. p53 is a sequence specific, DNA  
22 binding transcriptional activator [182, 183]. It is not required for normal cellular proliferation, but  
23 rather integrates signal transduction pathways that sense cellular stress, and thus has been  
24 referred to as a "guardian of the genome" [184]. Unlike the case with SV40 TAg, HPV E7, and  
25 Ad E1A, there is no structural similarity between SV40 TAg, HPV E6, and Ad E1B; this lack of  
26 structural similarity is reflected in the differences between their interactions with p53. The

1 metabolic half-life of p53 is extended in cells that express SV40 TAg or Ad E1B; consequently  
2 p53 levels are higher in these cells than in normal cells [185, 186]. On the other hand, p53  
3 levels in high-risk HPV E6 expressing cells are lower than in their normal counterparts [187,  
4 188], due to induction of p53 degradation through ubiquitin-mediated proteolysis [189].

5

### 6 **5.2.1. Human Papillomavirus (HPV)**

7 Papillomaviruses (PVs) are a group of small, non-enveloped, double-stranded DNA  
8 viruses that constitute the Papillomaviridae family. These viruses infect squamous epithelia of a  
9 variety of species [190]; to date, approximately 200 human papillomavirus (HPV) types have  
10 been described [191]. HPVs cause a range of epithelial hyperplastic lesions and can be  
11 classified into two groups: mucosal and cutaneous. These groups can be further divided into  
12 low- and high-risk, depending on the associated lesion's propensity for malignant progression.

13 The cutaneous HPVs 5 and 8 may be considered high-risk, as they are associated with  
14 a rare, genetically determined skin disease, epidermodysplasia verruciformis (EV). These  
15 lesions can progress to skin cancers particularly in sun-exposed areas of the body. Skin cancer  
16 in EV patients was the first HPV cancer type that was associated with HPV infections [192-196];  
17 More recent studies have revealed that HPV5 and 8 as well as related cutaneous HPVs may  
18 contribute to the development of non-melanoma skin cancers (NMSC), particularly in  
19 immunocompromised patients [197, 198]. Infections with cutaneous HPVs appear extremely  
20 frequently in the general population and some of these viruses, even the presumed high-risk  
21 HPV5, may be part of the normal "flora" of the skin as they can be detected in follicles of  
22 plucked hair [199, 200]. The mechanistic contributions of cutaneous HPVs and their interplay  
23 with other co-factors that may result in NMSC development remains the subject of intense study  
24 (reviewed in [201]). It has been shown that E6 proteins of cutaneous HPVs can target the  
25 proapoptotic Bcl-2 family member, Bak, for degradation. Bak plays an important role in signaling  
26 apoptosis in response the UV irradiation and hence it has been postulated that cutaneous HPV

1 expressing cells may be less prone to undergo apoptosis after UV induced DNA damage [202].  
2 This may lead to survival and expansion of HPV containing cells with extensive genomic  
3 aberrations, which may contribute to transformation. Some cutaneous HPVs exhibit bona fide  
4 transforming activities in cultured cells [203-206]. Moreover, skin hyperplasia and skin tumors  
5 develop in transgenic mice that express early region genes of cutaneous HPVs [207, 208]. HPV  
6 genomes are often found in only a subset of the cancer cells suggesting that either cutaneous  
7 HPVs may contribute to initiation of carcinogenesis but are not be required for maintenance of  
8 the transformed phenotype, or that they contribute to transformation through non cell  
9 autonomous mechanisms (reviewed in [201]).

10 The concept of low-risk and high-risk HPVs has been most clearly established with the  
11 mucosal HPVs. The low-risk mucosal HPVs, such as HPV6 and 11, cause genital warts,  
12 whereas the high-risk mucosal HPVs, such as HPV16 and 18, cause squamous intraepithelial  
13 lesions that can progress to invasive squamous cell carcinoma. HPV is also associated with  
14 oral and other anogenital malignancies, however, it is most commonly associated with cervical  
15 cancer; in fact, over 99% of all cervical cancers are associated with high-risk HPV infections.  
16 Both epidemiological and molecular evidence strongly supports the link between infection with  
17 high-risk HPVs and the development of cervical cancer. Nonetheless, the incidence of  
18 malignant progression of high-risk HPV associated lesions is relatively low; malignant  
19 progression usually occurs with other risk factors, such as decreased immune function, and/or  
20 after a long latency period after other genomic alterations in the host cell DNA have occurred.  
21 Smoking and prolonged use of birth control pills have also been implicated as risk factors for  
22 progression (reviewed in [209]). Maybe most intriguing, Fanconi anemia (FA) patients often  
23 develop squamous cell carcinomas at anatomical sites that are susceptible to HPV infections. It  
24 has been reported that oral carcinomas in FA patients are more frequently HPV positive than in  
25 the general population [210]. Hence, certain aberrations in the FA pathway may predispose to  
26 malignant progression of HPV associated lesions. Interestingly, the ability of HPV E7 to induce

1 genomic instability is increased in FA derived cells, thus providing a potential mechanistic  
2 rationalization for these findings [211]. The molecular mechanisms by which high-risk HPV  
3 causes cervical cancer have been studied extensively, and numerous viral and host interactions  
4 that may contribute to transformation and malignancy have been described (reviewed in [27]).

5         During carcinogenic progression the HPV genome frequently integrates into a host cell  
6 chromosome and, as a result, the viral oncoproteins, E6 and E7, are the only viral proteins that  
7 are consistently expressed in HPV positive cervical carcinomas. Viral genome integration is a  
8 terminal event for the viral life cycle and often results in deletion and/or mutation of other viral  
9 genes. Most significantly, expression of the transcriptional repressor E2 is often lost during  
10 integration. Moreover, the viral E6/E7 genes are expressed from spliced mRNAs that contain  
11 cellular sequences which results in increased mRNA stability. Hence, HPV genome integration  
12 is often associated with higher, dysregulated E6/E7 expression [212]. Persistent expression of  
13 E6 and E7 is necessary for maintenance of the transformed phenotype of cervical carcinoma  
14 cells [213, 214]. The expression of high-risk HPV E6 and E7 immortalizes primary human  
15 keratinocytes [215, 216], and when grown as organotypic “raft” cultures these cells display  
16 histopathological hallmarks of high-grade premalignant lesions [217]. However, these cells  
17 remain non-tumorigenic at low passages after immortalization; tumorigenic progression is not  
18 observed until long-term passaging in vitro or after the transduction of an additional oncogene  
19 [218-220]. Moreover, transgenic mice with expression of HPV E6 and E7 require low-dose  
20 estrogen for the development of cervical cancer [221]. This situation mimics the progression of  
21 high-risk HPV-positive cervical lesions, a process that occurs with a low frequency and requires  
22 the acquisition of additional host cellular mutations (reviewed in [222]).

23         HPVs have transforming properties in a number of rodent cell lines, and the transforming  
24 potential correlates with their clinical classification as high-risk and low-risk. Mutational  
25 analyses have revealed that E7 encodes the major transforming function [223-226], while E6  
26 does not score as a major transforming activity in most assays. High-risk HPV E7 also scores

1 in the classical oncogene cooperation assay in baby rat kidney cells [223, 227], whereas E6 can  
2 cooperate with ras in baby mouse kidney cells [228]. High-risk HPVs can extend the life span of  
3 primary human genital epithelial cells, and E6 and E7 are necessary and sufficient for this  
4 activity [226, 229-233]

5 As mentioned previously, the transforming activities of the high-risk E6 and E7  
6 oncoproteins is related to their ability to associate with and dysregulate cellular regulatory  
7 protein complexes, most notably p53 and pRB (reviewed in [155]). As p53 and pRB normally  
8 control cellular proliferation, differentiation, and apoptosis, the abrogation of their normal  
9 biological activities places such a cell at a risk of malignant progression.

10 In addition, high-risk HPV E6 and E7 expressing cells have a decreased ability to  
11 maintain genomic integrity [234]. The high-risk HPV E7 oncoprotein acts as a mitotic mutator  
12 and induces multiple forms of mitotic abnormalities, including anaphase bridges, unaligned or  
13 lagging chromosomes, and most notably multipolar mitoses [235]. Multipolar mitoses are  
14 histopathological hallmarks of high-risk HPV associated cervical lesions and cancer [236] and  
15 are caused by the ability of high-risk HPV to uncouple centrosome duplication from the cell  
16 division cycle [237, 238]. Hence, HPV E6/E7 oncoproteins mechanistically contribute to  
17 initiation and progression of cervical cancer (Figure 3).

### 18 19 **5.2.2. Hepatitis B Virus (HBV)**

20 It is estimated that over 400 million people worldwide are chronic carriers of HBV [239].  
21 The vast majority of infections are asymptomatic, and the non-cytopathic HBV [240] does not  
22 cause a significant immune response after the initial infection, presumably at least in part  
23 because HBV entry and expansion do not induce the expression of any cellular genes [142,  
24 241]. Nonetheless, HBV is a major etiological factor in the development of HCC, as 15-40% of  
25 infected individuals will develop chronic active hepatitis (CAH) which can in turn lead to  
26 cirrhosis, liver failure, or HCC [242, 243]. This development is accelerated by the exposure to

1 environmental carcinogens including aflatoxin B, cigarette smoke, and alcohol [146]. CAH is  
2 characterized by liver cell necrosis, inflammation, and fibrosis, and it is believed that the  
3 resulting cirrhosis may eventually lead to HCC due to the fact that the rapid regeneration of  
4 hepatocytes following constant necrosis may lead to the accumulation of mutations and the  
5 subsequent selection of cells with a carcinogenic phenotype [244]. Indeed, patients with  
6 cirrhosis are more likely to develop HCC than patients without cirrhosis [245, 246]. While it  
7 appears that both CAH and cirrhosis contribute to the development of liver carcinogenesis,  
8 there is also evidence, such as the correlation between serum HBV DNA level and risk of HCC  
9 [247], suggesting a direct oncogenic contribution of HBV to the carcinogenic process.  
10 Therefore, it appears that the cause of HBV-associated HCC is a combination of HBV encoded  
11 oncogenic activities along with the synergistic effects of chronic inflammation.

12 HBV has a circular, partially double-stranded, DNA genome with four overlapping open  
13 reading frames (ORFs) that encode for the envelope (preS/S), core (preC/C), polymerase, and  
14 X proteins [248]. Like retroviruses, the replication of HBV is dependent on reverse transcription;  
15 unlike retroviruses, integration of the viral genome into the host chromosome is not necessary  
16 for viral replication but does allow for persistence of the viral genome (reviewed in [249]). The  
17 integration event precedes tumor development, as the HBV genome is often found integrated in  
18 the host chromosome of patients with both CAH and HCC [250, 251]. HBV integration is a  
19 dynamic process, as chronic inflammation together with increased proliferation of hepatocytes  
20 may result in rearrangements of integrated viral and adjacent cellular sequences [245].  
21 Moreover, the integration event can result in chromosomal deletions and transpositions of viral  
22 sequences from one chromosome to another [252, 253]; consequently, HBV integration may  
23 result in genomic instability [254, 255] as well as activation of proto-oncogenes [256-260].  
24 However, integration of the HBV genome is not a necessary prerequisite for malignant  
25 progression as approximately 20% of patients with HBV-associated HCC do not display  
26 evidence of integration [250].

1 Examination of viral DNA sequences present in HCC has provided insight into additional  
2 oncogenic mechanisms of HBV. Sequences encoding the HBV X protein (HBx) and/or  
3 truncated envelope PreS2/S viral proteins are expressed in the majority of HCC tumor cells.  
4 Additionally, a novel viral hepatitis B spliced protein (HBSP) has been identified in HBV-infected  
5 patients [261]. However, the mere expression of such proteins does not confirm their role in  
6 HCC development and further studies are necessary to determine their potential contributions to  
7 HCC development.

8 HBx is a 154 amino acid multifunctional regulatory protein that is highly conserved  
9 among all of the mammalian hepadnaviruses [262], indicating that it likely plays an important  
10 role in the viral life cycle. The expression of HBx is maintained throughout all stages of  
11 carcinogenesis, including in cells with integrated HBV genomes [263-268]. Studies of HBx in  
12 cultured cells and transgenic animals support a role for HBx in transformation and have  
13 demonstrated that HBx functions as a regulatory protein for viral replication and, in the case of  
14 woodchuck hepatitis virus (WHV), is required for efficient infectivity [269-272]. In addition, in  
15 vitro and in vivo studies indicate that HBx plays an important role in the control of cell  
16 proliferation and viability [273-275]. The findings from studies of the biological functions of HBX  
17 can be summarized as follows: 1) The HBx protein acts on cellular promoters via protein-protein  
18 interactions and exhibits pleiotropic effects that modulate various cell responses to genotoxic  
19 stress, protein degradation, and signaling pathways (reviewed in [276]), ultimately affecting cell  
20 proliferation and viability [277, 278]. Specifically, HBx stimulates signal transduction pathways  
21 such as MAPK/ERK and can also upregulate the expression of genes such as c-Myc, c-Jun,  
22 NF- $\kappa$ B, AP-1, Ap-2, RPB5 subunit of RNA polymerase II, TATA binding protein, and CREB  
23 [279]. 2) HBx regulates proteasomal function [280-282]. 3) HBx affects mitochondrial function  
24 [283, 284]. 4) HBx protein modulates calcium homeostasis [285, 286]. 5) Expression of HBx  
25 causes genomic instability [287].

1 In addition to HBx, the HBV genome encodes a second group of regulatory proteins: the  
2 PreS2 activators [large surface proteins (LHBs) and truncated middle surface proteins (MHBs<sup>†</sup>)  
3 [288-291]. More than one-third of HBV-integrates in HBV related HCC encode functional MHBs<sup>†</sup>  
4 transactivators [292, 293], supporting the biological significance of PreS2 activators. The PreS2  
5 activators are derived from the HBV surface gene ORF, which consists of a single open reading  
6 frame divided into three coding regions, preS1, preS2, and S. Large (LHBs; preS1+preS2+S),  
7 middle (MHBs; preS2+S), and small (SHBs; S) envelope glycoproteins can be synthesized  
8 through alternate translational initiation [288, 290, 291]. The LHBs and MHBs<sup>†</sup> display  
9 transactivation activities; their transcriptional activator function is based on the cytoplasmic  
10 orientation of the PreS2 domain. PreS2 activators upregulate COX-2 and cyclin A and induce  
11 cell cycle progression [294]. Consistent with this notion, transgenic mice expressing MHBs<sup>†</sup> in  
12 the liver displayed increased hepatocyte proliferation rate and an increased occurrence of liver  
13 tumors [295].

14 In addition to sequences encoding for HBx and truncated envelope PreS2/S viral  
15 proteins, a novel viral hepatitis B spliced protein (HBSP) has been identified in HBV-infected  
16 patients [261]. The spliced HBV RNA encoding for HBSP can be reverse transcribed and  
17 encapsidated in defective HBV particles or expressed as HBSP [261]. HBSP induces apoptosis  
18 without cell-cycle block in an in vitro tissue culture model, and HBSP antibodies are present in  
19 the serum of 45% of chronic hepatitis patients [296]. Moreover, there seems to be a correlation  
20 between the presence of HBSP antibodies, viral replication and liver fibrosis [296].

21 HBV-associated liver carcinogenesis is viewed a multi-factorial process (Figure 4). The  
22 integration of the HBV genome into the host chromosome at early stages of clonal tumor  
23 expansion has been demonstrated to both affect a variety of cellular genes as well as exert  
24 insertional mutagenesis, while chronic liver inflammation confers the accumulation of mutations  
25 in the host genome. Additionally, HBV encoded HBx, PreS2 activators, and HBSP may exert  
26 oncogenic functions. However, exactly how these viral factors contribute to higher risks of HCC

1 development remains unclear. Further studies are necessary to reveal the molecular  
2 mechanisms underlying HBV-associated HCC development. Moreover, since host genomic  
3 background plays a role in the final disease outcome, an evaluation of the genetic factors in  
4 both the host and viral genome that cause a predisposition to hepatocarcinogenesis will help  
5 elucidate the carcinogenic mechanisms involved in HCC development.

### 7 **5.2.3. Epstein-Barr Virus (EBV)**

8 EBV is a ubiquitous double-stranded DNA virus of the  $\gamma$  herpesviruses subfamily of the  
9 lymphocryptovirus (LCV) genus. Worldwide, more than 95% of the population is infected with  
10 EBV [297, 298]; the majority of EBV infections occurs during childhood without causing overt  
11 symptoms. Post adolescent infection with EBV frequently results in mononucleosis, a self-  
12 limiting lymphoproliferative disease. EBV infects and replicates in the oral epithelium, and  
13 resting B lymphocytes trafficking through the oral pharynx become latently infected. Infected B  
14 lymphocytes resemble antigen activated B cells, and EBV gene expression in these cells is  
15 limited to a B cell growth program, termed Latency III, that includes LMP1, LMP2a/b, EBNA<sub>s</sub> -1,  
16 -2, -3a-3b, -3c, and -LP, miRNAs, BARTs, and EBERs. These cells are eliminated by a robust  
17 immune response to EBNA3 proteins, resulting in Latency I, a reservoir of latently infected  
18 resting memory B cells expressing only EBNA1 and LMP2. The differentiation of memory cells  
19 to plasma cells results in reactivation of the replication phase of the viral life cycle that includes  
20 expression of latency III gene products. In addition, there is likely another amplification step by  
21 re-infection of the epithelial cells followed by shedding virus in the saliva to the next host.

22 All phases of the EBV life cycle are associated with human disease. In  
23 immunocompromised individuals, infected cells increase in number and eventually B-cell growth  
24 control pathways are activated, inducing transformation and leading to malignancies such as  
25 NPC, BL, post-transplant lymphomas, and gastric carcinomas [3]. EBV-associated

1 malignancies follow distinct geographical distributions and occur at particularly high frequency in  
2 certain racial groups, indicating that host genetic factors may influence disease risk [299, 300].  
3 EBV encodes several viral proteins that have transforming potential, including EBV latent  
4 membrane protein 1 and 2 (LMP1 and LMP2) and EBV nuclear antigen 2 and 3 (EBNA2 and  
5 EBNA3). LMP1 can transform a variety of cell types, including rodent fibroblasts [301], and is  
6 essential for the ability of EBV to immortalize B cells [302]. The multiple transmembrane-  
7 spanning domains and the carboxyl terminus of LMP1 can interact with several tumor necrosis  
8 factor receptor associated factors (TRAFs) [303, 304]; this interaction results in high levels of  
9 activity of NF- $\kappa$ B, Jun, and p38 in LMP1-expressing epithelial and B cells [305-307]. Through  
10 NF- $\kappa$ B, LMP1 provides survival signals by inducing Bcl-2 family members, c-FLIP, c-IAPs, and  
11 adhesion molecules [308]. LMP1 also upregulates the expression of numerous anti-apoptotic  
12 and adhesion genes and activates the expression of IRF-7 [309], matrix metalloproteinase-9  
13 (MMP-9) and fibroblast growth factor-2 (FGF-2) [310]. A second viral membrane protein, LMP2,  
14 is dispensable for transformation of naïve B cells but is required for transformation of post-  
15 germinal center B cells. LMP2 interacts with Lyn and Syk to mimic B-cell-receptor (BCR)  
16 signaling, including activation of the PI3K/AKT survival pathway [311].

17 Other viral genes involved in transformation include EBNA2 and EBNA3. EBNA2, one of  
18 the first latent proteins to be detected after EBV infection together with EBNA-LP, is a  
19 promiscuous transcriptional activator of both cellular and viral genes [312, 313] and is essential  
20 for B-cell transformation [314]. EBNA3A, 3B, and 3C are hydrophilic nuclear transcriptional  
21 regulators. EBNA3A and EBNA3C are essential for B-cell transformation in vitro, whereas  
22 EBNA3B is dispensable [315]. All three EBNA3 proteins can suppress EBNA2-mediated  
23 transactivation [316].

24 An excellent cell culture model system exists for the study of EBV. In vitro infection of  
25 human peripheral blood B cells results in the long-term growth of EBV transformed

1 lymphoblastoid cell lines (LCLs). These cell lines express Latency III gene products which co-  
2 opt cellular pathways to effect cell growth. LMP1 mimics CD40 to activate NF- $\kappa$ B, LMP2 mimics  
3 the B cell antigen receptor, and EBNA-2, -LP, -3A, -3B, and -3C mimic activated Notch. These  
4 pathways are constitutively active and drive proliferation through a normal cell cycle cascade.  
5 Moreover, there are no additional mutations to the RB or p53 pathways. Finally, if EBV signals  
6 are removed, the cells stop proliferating; when LMP1 or EBNA2 expression is restored, the cells  
7 begin to proliferate again. A summary of the role of EBV in carcinogenesis is depicted on  
8 Figure 5.

#### 10 **5.2.4. Kaposi's Sarcoma-associated herpesvirus (KSHV)/Human Herpes Virus 8** 11 **(HHV8)**

12 HHV8, also known as KSHV, is a recently discovered [18] double-stranded human  
13 rhadinovirus of the  $\gamma$ -herpesvirus subfamily and, like other  $\gamma$ -herpesviruses, establishes lifelong  
14 latency in B cells. KSHV is associated with all forms of KS, primary effusion lymphomas  
15 (PELs), and multicentric Castlemans disease (MCD) [18, 317-319]. The neoplastic potential of  
16 KSHV, especially in immunocompromised individuals, is well established: epidemiological  
17 studies link KSHV to human malignancies [3], KSHV transforms endothelial cells [320], and  
18 KSHV encoded transforming genes have been identified. The current model of KSHV-induced  
19 malignancy involves a combination of proliferation, survival, and transformation mediated by  
20 latently expressed viral proteins together with a paracrine mechanism that is exerted directly or  
21 indirectly by the lytically expressed v-cytokines and viral G-protein coupled receptor (vGPCR)  
22 (Figure 6). HIV-1 infected individuals are at the highest risk for developing KS. Interestingly, KS  
23 lesions and tumors appear to regress in patients who receive Highly Active Antiretroviral  
24 Therapy (HAART), suggesting that KSHV gene expression may be insufficient to initiate or  
25 maintain transformation [321, 322].

1 KS is an angioproliferative disease involving numerous angiogenic factors, endothelial  
2 cell (EC) growth factors, and pro-inflammatory cytokines, including viral factors such as vIL-6,  
3 vCCL-1, 2, and 3, and viral G protein-coupled receptor (vGPCR). VEGF is induced by vIL6 and  
4 subsequently promotes angiogenesis, and mouse cell lines that stably express vIL-6 and  
5 secrete high levels of VEGF and are tumorigenic in nude mice [323]. A notable property of the  
6 v-chemokines are their pro-angiogenic activities [324, 325]. Finally, vGPCR may contribute to  
7 KSHV-associated neoplasia by inducing and sustaining cell proliferation [326-330].

8 Latency expressed KSHV proteins that promote cell proliferation and survival and thus  
9 may contribute to cellular transformation include the ORF73-71 locus-encoded latency  
10 associated antigen (LANA, ORF73), viral cyclin (v-cyclin, ORF72), viral FLICE inhibitory protein  
11 (vFLIP, ORF71), viral interferon regulatory factor 1 (vIRF-1), and the Kaposin/K12 gene. LANA  
12 stimulates cellular proliferation and survival [331, 332], v-cyclin induces cell cycle progression  
13 [333], vFLIP and vIRF3 mediate pro-survival signaling [334, 335], and kaposins induce cytokine  
14 expression and cell growth [336].

15 In addition to the viral cytokines, vGPCR, and the five latency genes mentioned, there  
16 are two KSHV-encoded constitutive signaling membrane proteins, variable ITAM-containing  
17 protein (VIP) and latency associated membrane protein (LAMP), that play a role in KSHV-  
18 associated malignancies. VIP is encoded by the K1 ORF and can transform rodent fibroblasts,  
19 which, when injected into nude mice, induce multiple and disseminated tumors [337]. VIP can  
20 also functionally substitute for the saimiri transformation protein (STP) of herpesvirus saimiri  
21 (HVS) to induce lymphomas in common marmoset monkeys and transgenic animals expressing  
22 VIP develop lymphomas and sarcomas [338]. In addition to its direct transforming functions,  
23 VIP can induce angiogenic factors and inflammatory cytokines [116]. LAMP, which is encoded  
24 by the K15 ORF, exhibits potential mitogenic and survival signaling via Src-family kinases and  
25 NF- $\kappa$ B activation and may promote cell survival via interaction with the Bcl-2 related anti-  
26 apoptotic protein HAX-1 [339].

1 Finally, KSHV also contains several immune-evasion genes, including MIR1, MIR2,  
2 vIRFs, Orf45, and complement control protein homolog (CCPH). The KSHV K3 and K5  
3 proteins, MIR1 and MIR2, downregulate MHC I expression, thus inhibiting viral antigen  
4 presentation. The KSHV vIRFs and Orf45 inhibit the host interferon response, while CCPH  
5 inhibits complement-mediated lysis of infected cells (reviewed in [327, 340]). Together, these  
6 immune evasion proteins ensure life-long viral persistence in the host, and consequently  
7 contribute to KSHV-associated pathogenesis.

## 8 9 **6. Viruses Implicated in Human Cancers**

10 In addition to the above viruses and cancers, there also exist a number of other cancers  
11 that may have an infectious etiology. A causal role for these viruses in human malignancies  
12 remains to be fully addressed; current knowledge regarding these viruses and their potential  
13 role in human cancer will be summarized in the following sections.

### 14 15 **6.1. Polyomaviruses**

16 The Polyomaviridae family is a group of non-enveloped, small double-stranded DNA  
17 viruses that have been isolated from humans, monkeys, rodents, and birds. The first  
18 polyomavirus to be discovered, mouse polyoma virus [9, 341], is one of the most aggressive  
19 carcinogenic viruses and causes tumors in almost every tissue (poly-oma) of susceptible mouse  
20 strains [342, 343]. Although it does not cause malignancies in humans, mouse polyoma virus  
21 has been thoroughly studied and has been instrumental in the establishment of systems for the  
22 study of numerous eukaryotic cellular processes [344]. The second polyomavirus discovered,  
23 SV40, was isolated as a contaminant of early batches of the polio vaccine, which was produced  
24 in African green monkey kidney cells [39]. SV40 naturally infects the rhesus monkey where it  
25 establishes a low-level infection and persists in the kidneys without any noticeable effects.

1 SV40 is closely related to two human polyomaviruses, BKV and JCV, which were discovered in  
2 1971 from the urine of a renal transplant patient [40] and the brain of a patient with progressive  
3 multifocal leukoencephalopathy [42], respectively. Infection with BKV and JCV is widespread in  
4 humans and is usually subclinical. However, in immunosuppressed patients, BKV is associated  
5 with renal nephropathy [345, 346] and JCV can cause progressive multifocal  
6 leukoencephalopathy (PML) [347, 348]. More recently two additional novel putative human  
7 polyomaviruses, termed KI and WU, have been isolated [349, 350].

8 SV40, BKV, and JCV can all transform cells in vitro and induce tumors in rodents;  
9 additionally, the injection of polyomavirus transformed cells in animal models or the ectopic  
10 expression of polyomavirus regulatory proteins in transgenic animals also induces tumors  
11 (reviewed in [40, 41, 351]). Together, these findings demonstrate the oncogenic potential of the  
12 polyomaviruses. However, the association of these polyomaviruses with human malignancy  
13 remains controversial.

14 A number of studies have implicated SV40 in a range of human cancers, including  
15 mesothelioma, osteosarcoma, non-Hodgkin lymphoma (NHL), and a variety of childhood brain  
16 tumors. On the other hand, other studies have failed to demonstrate an association of SV40  
17 with human cancer, and the question of whether the release of SV40 into the human population  
18 through the polio vaccine contributed to the development of human cancers remains a  
19 contentious issue. Although in the 1950s approximately 100 million people were exposed to  
20 SV40 through the polio vaccine in the US alone, there is currently no evidence to suggest that  
21 SV40 infection is widespread among the population or that there is an increase in tumor burden  
22 among individuals who received the contaminated vaccine. Recently, studies have suggested  
23 that flawed detection methods may account for many of the positive correlations of SV40 with  
24 human tumors. In summary, the studies performed to date have failed to provide conclusive  
25 proof implicating SV40 as a human pathogen [352, 353].

1 Like SV40, a role for BKV and JCV in human tumors has been suggested, however, no  
2 conclusive proof exists that either virus directly causes or acts as a cofactor in human cancer.  
3 The search for a correlation between BKV and JCV and human cancer is complicated due to  
4 the fact that both viruses are ubiquitous in the population. With respect to JCV, there have been  
5 reports of JCV variants in a variety of human brain tumors; these studies have not, though,  
6 demonstrated any causal effects (reviewed in [354]). There is also correlative data regarding  
7 the potential role of BKV in human cancer. BKV persistently infects epithelial cells in the urinary  
8 tract, and some studies have linked BK virus infections to prostate cancer [355].

## 10 **6.2. Adenoviruses**

11 Members of the Adenoviridae family cause lytic and persistent infection in a range of  
12 mammalian and avian hosts. In humans, more than 50 different adenovirus serotypes have  
13 been described. They can be divided into six species, designated A-F [356]. Generally,  
14 clinically inapparent infection with these viruses occurs during early childhood, and tonsillar  
15 lymphocytes or peripheral blood lymphocytes remain persistently infected [357, 358]. Although  
16 certain Ad serotypes are highly transforming in cell culture and in animal models, early studies  
17 indicated that these viruses may not associated with human cancers [359-361]. This issue has  
18 been recently readdressed, however, and one study reported detection of adenovirus DNA in  
19 pediatric brain tumors [362]. However, a possible causal relationship of Ad infection with the  
20 pathogenesis of malignant brain tumors still remains unclear.

21 The transforming and oncogenic potential of adenoviruses has been traditionally  
22 ascribed to the E1A and E1B oncoproteins, which are similar to SV40 TAg and high-risk HPV  
23 E7/E6 target pRb and p53, respectively. However, more recent studies have suggested that, at  
24 least with some serotypes, E4 ORFs may contribute to cellular transformation [363], potentially  
25 through a “hit-and-run” mechanism [364]. Hence, the possible contribution of adenovirus  
26 infections to some aspects of human tumor development may need to be carefully re-evaluated.

1

### 2 **6.3. Human Endogenous Retroviruses (HERVs)**

3       HERVs are sequences within the genome that resemble infectious retroviruses  
4 (reviewed in [43, 44, 365]) that result from ancestral exogenous retroviral infections that became  
5 incorporated into the germ line DNA. Today, HERVs constitute ~8% of genome [366] and  
6 possess a similar genomic organization to exogenous complex retroviruses such as human  
7 immunodeficiency virus (HIV) and HTLV. Evolutionary pressure has ensured the inactivation of  
8 HERVs, leading to the idea that HERVs are merely “junk DNA”. However, recent evidence  
9 suggests that some HERVs may have both physiological and pathological roles, including roles  
10 in human malignancy.

11       While the exact role(s) of HERVs has yet to be fully elucidated, some studies have  
12 suggested that HERVs might play a role in carcinogenesis. Specifically, some HERVs have  
13 been implicated in human malignancy, due mainly to the increased expression of the HERV  
14 mRNA [367], functional protein [368], and retrovirus-like particles [369] in certain cancers.  
15 HERVs may also be linked to the generation of new promoters [370] or the activation of proto-  
16 oncogenes [371].

17       Current studies focus on the association of HERV-K with a number of cancers, including  
18 germ cell tumors, in particular seminomas [368, 372], breast cancer, myeloproliferative disease,  
19 ovarian cancer [373], melanoma [374, 375], and prostate cancer [376]. Some seminomas have  
20 been reported to express HERV-K proteins and sometimes release defective viral particles  
21 [369]. HERV-K proteins Rec and Np9 can bind the promyelocytic leukemia zinc finger (PLZF)  
22 protein [377], and hence it has been suggested that HERV-encoded proteins may contribute to  
23 the carcinogenic process.

24       None of these studies, however, provides compelling evidence that HERV-K expression  
25 contributes to tumorigenesis and it is equally possible that HERV gene expression may merely  
26 represent a corollary of cell transformation.

1 Recently, it has been discovered that recurrent chromosomal translocations importantly  
2 contribute to the development of human solid tumors. Interestingly, some of these translocations  
3 result in HERV-K regulatory sequences being placed upstream of the coding sequences of ETS  
4 transcription factor family members. Since HERV-K regulatory sequences are androgen  
5 responsive, such translocations cause aberrant, androgen-induced expression of these ETS  
6 transcription factors [376]. This is an exciting finding as the result of such translocations is  
7 conceptually similar to insertional mutagenesis, where retroviruses contribute to carcinogenesis  
8 by integrating in the vicinity of cellular proto-oncogenes, thereby causing their aberrant  
9 expression.

#### 11 **6.4. Human Mammary Tumor Virus (HMTV)/Pogo Virus**

12 The idea of the existence of a human breast cancer virus followed Bittner's  
13 demonstration that a virus, MMTV, can cause breast cancer in mice [378]. While studies in the  
14 last 7 decades have failed to provide compelling evidence proving this model, a possible viral  
15 etiology for some breast cancers remains an active and controversial area of research. A  
16 number of reports have suggested that an MMTV-related virus, human mammary tumor virus  
17 (HMTV), sometimes also referred to as the Pogo virus, may be associated with human breast  
18 cancers (reviewed in [45]).

19 A 660-bp sequence similar to the MMTV env gene was reportedly detected in 38% of  
20 American women's breast cancers [379]; subsequent polymerase chain reaction (PCR)  
21 amplifications detected other gene segments homologous to MMTV [380]. Moreover, env and  
22 LTR HMTV genes have been found inserted into several chromosomes [381], reminiscent of  
23 MMTV, which induces oncogenesis via insertional mutagenesis. The entire HMTV genome,  
24 which contains hormone response elements, has also been detected in fresh breast cancers  
25 [381]; additionally, primary breast cancer cells produce HMTV particles in vitro [382];

1 additionally, HMTV particles with morphogenic and molecular characteristics similar to MMTV  
2 were reported in primary breast cancer cells [382]. However, other groups have been unable to  
3 detect such sequences in breast cancers [383].

4         Since many HERVs are similar to MMTV, it is not clear whether HMTV represents an  
5 infectious entity, and/or if it can be acquired from infected mice as has been suggested by an  
6 epidemiological study, which reported that regions where *Mus domesticus* infestations are  
7 prevalent have the highest incidence of human breast cancer [384]. In possible support of an  
8 infectious etiology, human MMTV receptor-related proteins have been cloned [385]. Moreover,  
9 it has recently been reported that MMTV replicates rapidly and successfully in human breast  
10 cancer cells [386].

11         Even if HMTV-like sequences are indeed expressed in some human breast cancers,  
12 there is presently no compelling evidence that unambiguously supports a mechanistic  
13 contribution of such viruses to breast cancer development.

14

#### 15 **6.5. Xenotropic murine leukemia virus-related virus (XMRV)**

16         The finding that the familial prostate cancer susceptibility locus *Hpc1* is linked to  
17 mutations in the structural gene for RNase L [387], an effector in the interferon induced innate  
18 viral response [388], led to the suggestion that inherited defects in RNase L might allow for  
19 infection with an oncogenic virus, thus leading to the development of PC. Xenotropic murine  
20 leukemia virus-related virus (XMRV) is a recently described gamma retrovirus that was  
21 discovered using PCR cloned codas from tumors from PC patients with a mutation in RNase L  
22 [389]. XMRV protein was detected in the stroma and hematopoietic cells of the prostate tumors,  
23 but was not detected in the actual cancer cells [389]. Therefore, it is unclear whether XMRV  
24 may be causally associated with prostate cancer. However, it is possible that XMRV may  
25 contribute to tumorigenesis through an indirect mechanism.

1

## 2 **6.6. Torque teno virus (TTV)**

3 Torque teno virus (TTV) is a single-stranded circular DNA virus of the Circoviridae family  
4 and was first found in a patient with non-A-E-hepatitis [46]. Since its initial discovery, a large  
5 number of TTV types and subtypes that display substantial genomic variation have been  
6 described [390-395]. TTV is acquired in early childhood [396, 397] and remains prevalent in  
7 adults [391, 398, 399]. Numerous attempts to link TT viruses to pathogenicity, particularly liver  
8 diseases, have thus far been unsuccessful [400-402]. However, one study did suggest that a  
9 high TTV load may have prognostic significance in HCV-associated liver disease, but the issue  
10 of whether high TTV load mediates HCV-associated disease progression remains to be  
11 addressed. Another study demonstrated a relatively high prevalence of TTV-related DNA  
12 sequences in human cancers, specifically gastrointestinal cancer, lung cancer, breast cancer,  
13 and myeloma [403]. No causal relationship between TTV infection and carcinogenesis can be  
14 drawn from this study, as normal control tissues were not included.

15

## 16 **7. Concluding Remarks/Perspectives**

17 The study of virus-associated cancers has provided many critical insights into key  
18 mechanisms of carcinogenesis. The initial work that showed that some animal cancers were  
19 caused by retroviruses firmly established the concept that cancers can be caused by infectious  
20 agents. Analyses of retroviral integration sites and retrovirally transmitted transforming genes  
21 yielded a treasure trove of information on oncogenes and tumor suppressors that were later  
22 found to be similarly mutated in human malignancies. While there is no firm evidence that  
23 human tumors are caused by retroviral transmission of activated oncogenes, these studies,  
24 nevertheless, provided much of the foundation of modern oncology.

1           The main difference between these early studies with transforming animal retroviruses  
2 and human tumor viruses is that oncogenes of human tumor viruses are viral genes, rather than  
3 mutated versions of cellular genes that were accidentally assimilated during the viral replication  
4 cycle. These human tumorvirus oncogenes play central roles in viral life cycles and their  
5 oncogenic potential is a manifestation of these activities.

6           Some viruses, most notably the high-risk HPVs, play essential roles in the initiation as  
7 well as progression of cancers and continued expression of their viral transforming activities is  
8 necessary for the maintenance of the transformed phenotype. This concept is supported by  
9 studies that showed that the major targets of the HPV E6 and E7 oncoproteins, the p53 and  
10 pRB tumor suppressors, are retained in a dormant, yet functional state, in HPV positive cervical  
11 cancer cell lines, whereas the pRB and p53 tumor suppressor sustained mutations in HPV  
12 negative cervical carcinoma lines [188]. Hence, these proteins are predicted to be excellent  
13 targets for therapy. This concept is impressively supported by numerous studies that showed  
14 that cervical cancer cell lines that are manipulated to lose E6/E7 oncogene expression promptly  
15 undergo growth arrest, senescence, and/or apoptosis and that this is related to reactivation of  
16 the p53 and pRB tumor suppressor pathways [213].

17           Since HPV E6 and E7 lack intrinsic enzymatic activities, the development of E6/E7  
18 specific antivirals is difficult. HPV E6 and E7, like many viral oncoproteins, function by  
19 associating with host cellular proteins, including enzymes such as ubiquitin ligases and histone  
20 modifying enzymes. It will be important to determine whether targeting such enzymes will have  
21 a specific therapeutic benefit [404]. Last, but not least, viral proteins that are consistently  
22 expressed in virus-associated tumors are attractive targets for development of therapeutic  
23 vaccination strategies.

24           It will also be interesting to explore whether the alterations in cell signaling networks due  
25 to viral oncogene expression renders infected cells uniquely dependent on (“addicted to”)  
26 specific cellular signal transduction pathways. The concept of synthetic lethality in yeast predicts

1 that such pathways may be excellent candidates for therapeutic intervention [405]. The  
2 availability of genome wide RNAi and cDNA libraries should make such approaches feasible.  
3 Given that the pathways targeted by viral oncoproteins are often mutated in non-virus  
4 associated cancers, one might predict that such studies may reveal viable therapeutic targets  
5 for numerous malignancies.

6 In some cases, however, the virus may only contribute to one specific step in the  
7 carcinogenic process and its continued expression may thus not be necessary for the  
8 maintenance of the transformed state. This is sometimes referred to as “hit-and-run”  
9 carcinogenesis. In these cases, it is very difficult to conclusively demonstrate that the virus  
10 indeed did contribute to the development of a given tumor. The relatively recent realization that  
11 some viruses encode proteins that subvert genomic stability lends some mechanistic credence  
12 to this model (reviewed in [27]). Accordingly, a virus-infected cell would be significantly more  
13 promiscuous for accumulation of genetic aberrations that eventually may lead to tumor  
14 formation. One might also imagine that viral proteins that alter the histone code may  
15 permanently modify the epigenetic imprint of a host cell and the resulting alterations in gene  
16 expression may contribute to cellular transformation.

17 Another possibility is that viral gene expression is only maintained in some tumor cells.  
18 This has been observed with some HPV containing non-melanoma skin cancers [201]. While  
19 this is consistent with a “hit-and-run” mechanism, it may also indicate that viral oncogene  
20 expression might provide a growth promoting activity indirectly through secreted factors that are  
21 necessary for optimal tumor growth.

22 Conversely, the mere presence of viral sequences in a given cancer type does not  
23 necessarily imply that the virus mechanistically contributes to the genesis of the tumor. It may  
24 simply represent the fact that tumor cells represent a particularly fertile ground for viral  
25 replication. Tumors often contain a larger population of proliferative cells than the surrounding  
26 normal tissue and hence might be particularly permissive for viral replication. In addition, they

1 often are subject to decreased surveillance by the immune system. Given the availability of new  
2 tools to discover virus sequences in tumors, this issue will represent a major challenge for the  
3 future.

4 Host defense mechanisms play a significant role in modulating viral carcinogenesis.  
5 Their protective role is most clearly illustrated by the fact that Epstein-Barr virus in most cases  
6 establishes life long asymptomatic latency and tumors arise when immunesurveillance of the  
7 host organism is weakened or fails. Similarly, non-melanoma skin cancers associated with  
8 cutaneous HPV infections are a frequent complication in organ transplant patients.

9 However, in other cases the host response to viral infection and/or their cellular  
10 consequences significantly contributes to the carcinogenic process. While infection of liver cells  
11 with hepatitis viruses does not appear to cause a major immune response to the initial infection  
12 it causes extensive inflammation. This causes cell damage and production of genotoxic reactive  
13 oxygen species, which in concert with rapid proliferation due to regenerative processes and  
14 potentially genomic destabilization due to viral gene expression, may lead to accumulation of  
15 mutations that eventually lead to carcinogenic progression.

16 The infectious etiology of certain cancers affords the unique possibility for prophylactic  
17 vaccination. Since vaccination with a weakened live virus is not an option for oncogene carrying  
18 viruses, it is necessary to develop “subunit vaccines” consisting of immunogenic recombinant  
19 viral proteins. Such a vaccine has been developed for HBV and has proven highly efficacious.  
20 HBV vaccines are relatively inexpensive; consequently, they are widely used and have had a  
21 remarkable public health impact. Prophylactic vaccines to prevent infections with the most  
22 abundant low-risk and/or high-risk HPVs (HPV6, HPV11 and/or HPV16, HPV18) are now  
23 commercially available. These vaccines consist of recombinant L1 proteins that form virus-like  
24 particles (VLPs), which induce a vigorous type-specific immune response and show great  
25 promise (reviewed in [406]). Vaccination has to be before the onset of sexual activity and it will  
26 be important to determine how long the protection will last. However, since HPV-induced

1 cervical carcinogenesis is a slow process, it will be several decades before there will be a  
2 noticeable decrease in cervical cancer cases due to vaccination [407]. It will also be important to  
3 determine whether other high-risk HPVs that are not targeted by the current vaccine  
4 preparations will fill the void and become more abundant in the population. This would require  
5 development and inclusion of VLPs corresponding to additional HPV types to the vaccine  
6 preparations. Perhaps most significant, these vaccines are extraordinarily expensive to  
7 produce. Since most cervical cancer cases and deaths occur in medically underserved patients,  
8 it is thus unlikely that the population that would profit the most from a prophylactic approach will  
9 gain access to these vaccines in the near future.

10

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18

19

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1 **Figure Legends**

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3 **Figure 1:** Schematic depiction of the major biological activities that contribute to the  
4 transforming activities of HTLV-1. See text for details.

5

6 **Figure 2:** Schematic depiction of the major biological activities that contribute to the  
7 transforming activities of HCV. See text for details.

8

9 **Figure 3:** Schematic depiction of the major biological activities that contribute to the  
10 transforming activities of high-risk mucosal HPVs. See text for details.

11

12 **Figure 4:** Schematic depiction of the major biological activities that contribute to the  
13 transforming activities of HBV. See text for details.

14

15 **Figure 5:** Schematic depiction of the major biological activities that contribute to the  
16 transforming activities of EBV. See text for details.

17

18 **Figure 6:** Schematic depiction of the major biological activities that contribute to the  
19 transforming activities of HHV-8/KSHV. See text for details.

20

**Table 1. Evans and Mueller guidelines [21]**

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**Epidemiologic guidelines**

1. Geographic distribution of viral infection corresponds with that of the tumor, adjusting for the presence of known cofactors
2. Viral markers are higher in case subjects than in matched control subjects
3. Viral markers precede tumor development, with a higher incidence of tumors in persons with markers than those without
4. Tumor incidence is decreased by viral infection prevention

**Virologic guidelines**

1. Virus can transform cells *in vitro*
  2. Viral genome is present in tumor cells, but not in normal cells
  3. Virus induces the tumor in an experimental animal
- 

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**Table 2. Hill criteria for causality [22,23]**

- 
1. **Strength of association** (how often is the virus associated with the tumor?)
  2. **Consistency** (has the association been observed repeatedly?)
  3. **Specificity of association** (is the virus uniquely associated with the tumor?)
  4. **Temporal relationship** (does virus infection precede tumorigenesis?)
  5. **Biologic gradient** (is there a dose response with viral load?)
  6. **Biologic plausibility** (is it biologically plausible that the virus could cause the tumor?)
  7. **Coherence** (does the association make sense with what is known about the tumor?)
  8. **Experimental evidence** (is there supporting laboratory data?)
- 

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Table 3. Properties of human tumor viruses

Virus	Viral Taxonomy	Genome	Cell Tropism	Human Cancers
EBV	Herpesviridae	dsDNA 172 kb ~90 ORFs	Oropharyngeal epithelial cells, B- cells	BL, NPC, lymphomas
HBV	Hepadnaviridae	dsDNA 3.2 kb 4 ORFs	Hepatocytes, white blood cells	HCC
HCV	Flaviviridae	dsRNA 9.4 kb 9 ORFs	Hepatocytes	HCC
HPV	Papillomaviridae	dsDNA 8 kb 8-10 ORFs	Squamous epithelial cells	Cervical, oral, and anogenital cancer
HTLV-1	Retroviridae	dsRNA 9.0 kb 6 ORFs	T-cells	ATL
KSHV	Herpesviridae	dsDNA 165 kb ~90ORFs	B-cells	Kaposi sarcoma, primary effusion lymphoma

ATL, adult T-cell leukemia; BL, Burkitt's lymphoma; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HPV, human papillomavirus; HTLV-1, human T-cell leukemia virus; KSHV, Kaposi's sarcoma-associated herpesvirus; NPC, nasopharyngeal carcinoma

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**Table 4. Properties of viruses implicated in human cancers**

<b>Virus</b>	<b>Viral Taxonomy</b>	<b>Genome</b>	<b>Human Cancers</b>
BKV	Polyomaviridae	dsDNA ~5.2 kb	Prostate?
JCV	Polyomaviridae	dsDNA ~5.2 kb	Brain?
SV40	Polyomaviridae	dsDNA ~5.2 kb	Brain, bone, mesothelioma?
HERVs	Retroviridae	dsRNA/DNA?	Seminomas, breast, ovarian, melanoma?
HMTV	Retroviridae	dsRNA/DNA?	Breast?
TTV	Circoviridae	ssDNA 3.8 kb	Gastrointestinal, lung, breast, and myleoma?

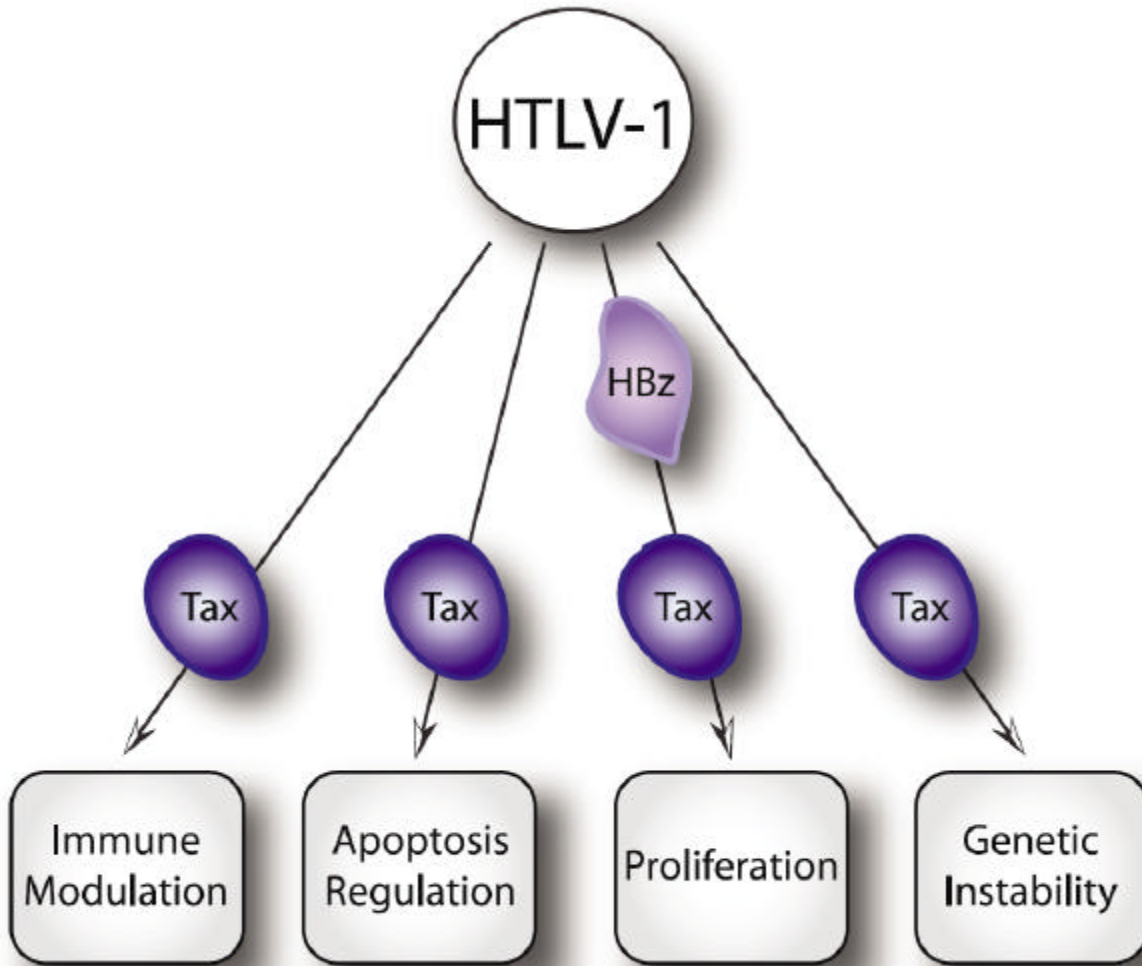
BKV, BK virus; HERVs, human endogenous retroviruses; HMTV, human mammary tumor virus; JCV, JC virus; SV40, simian virus 40; TTV, Torque Teno virus

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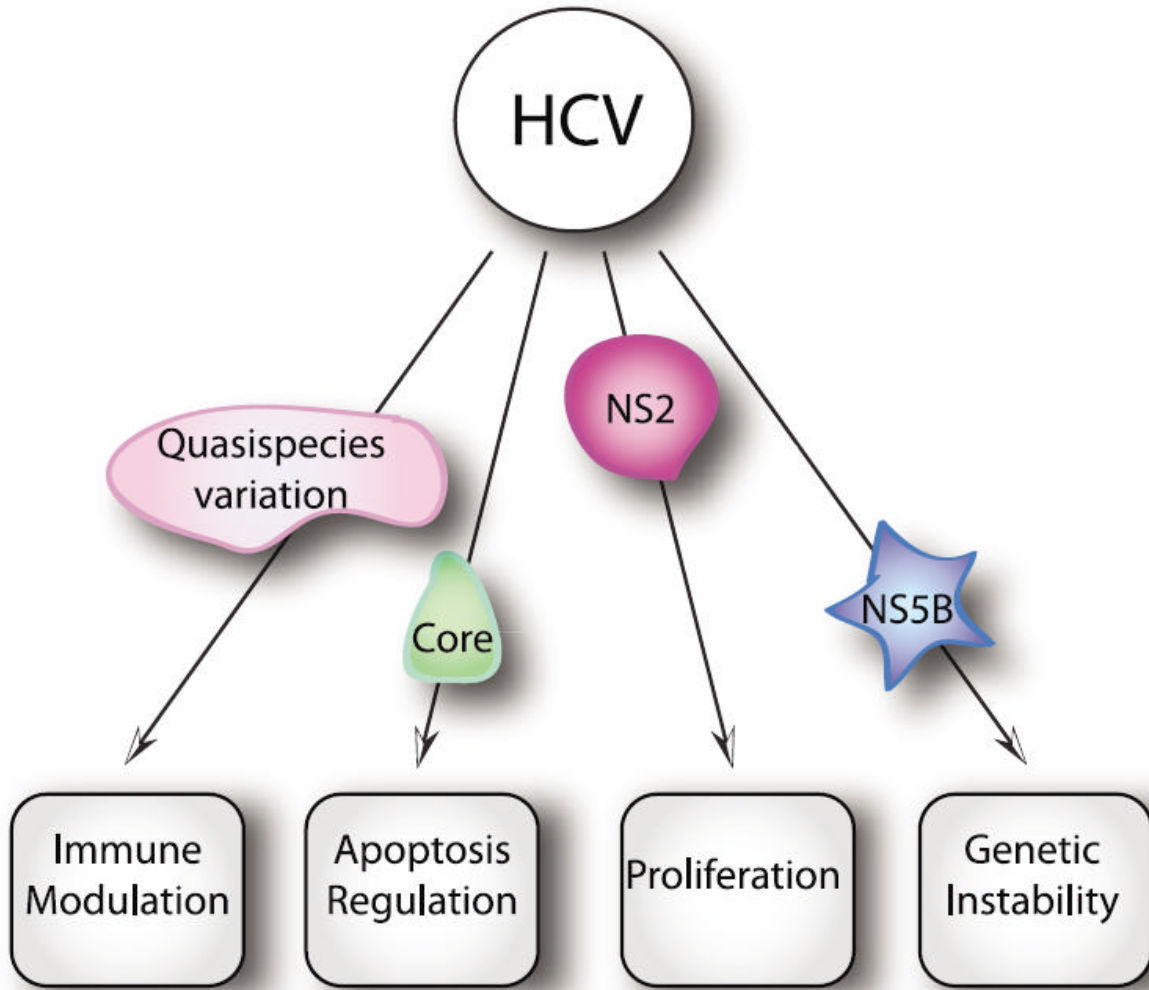


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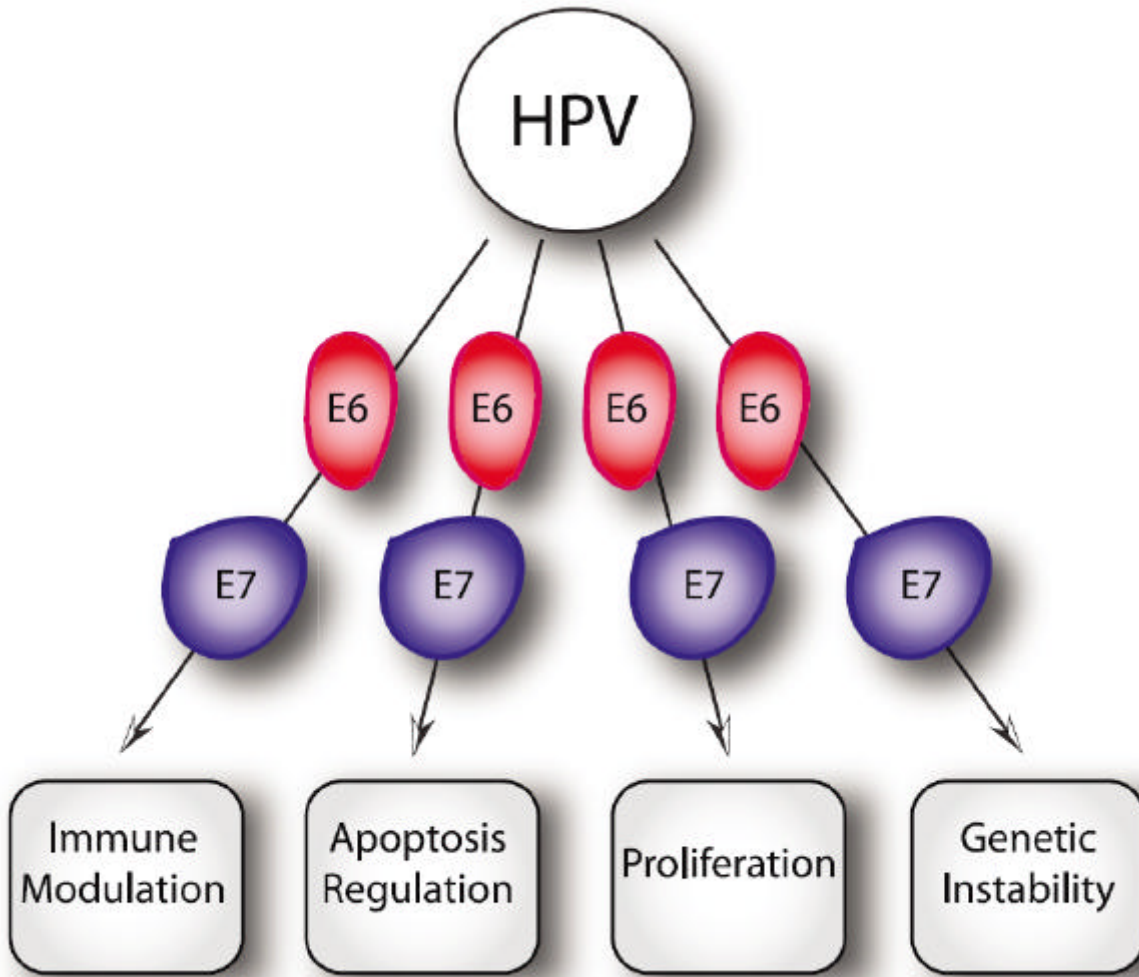


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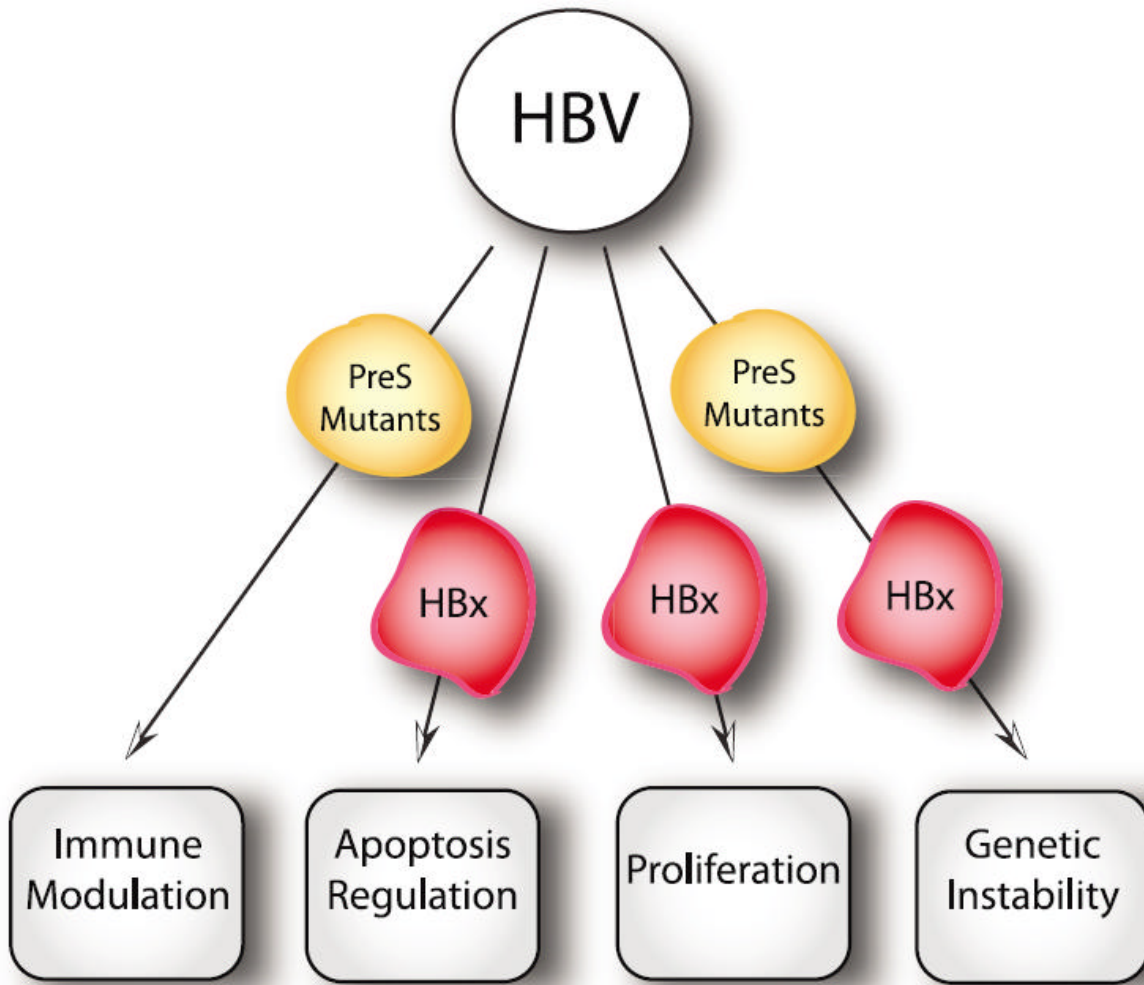


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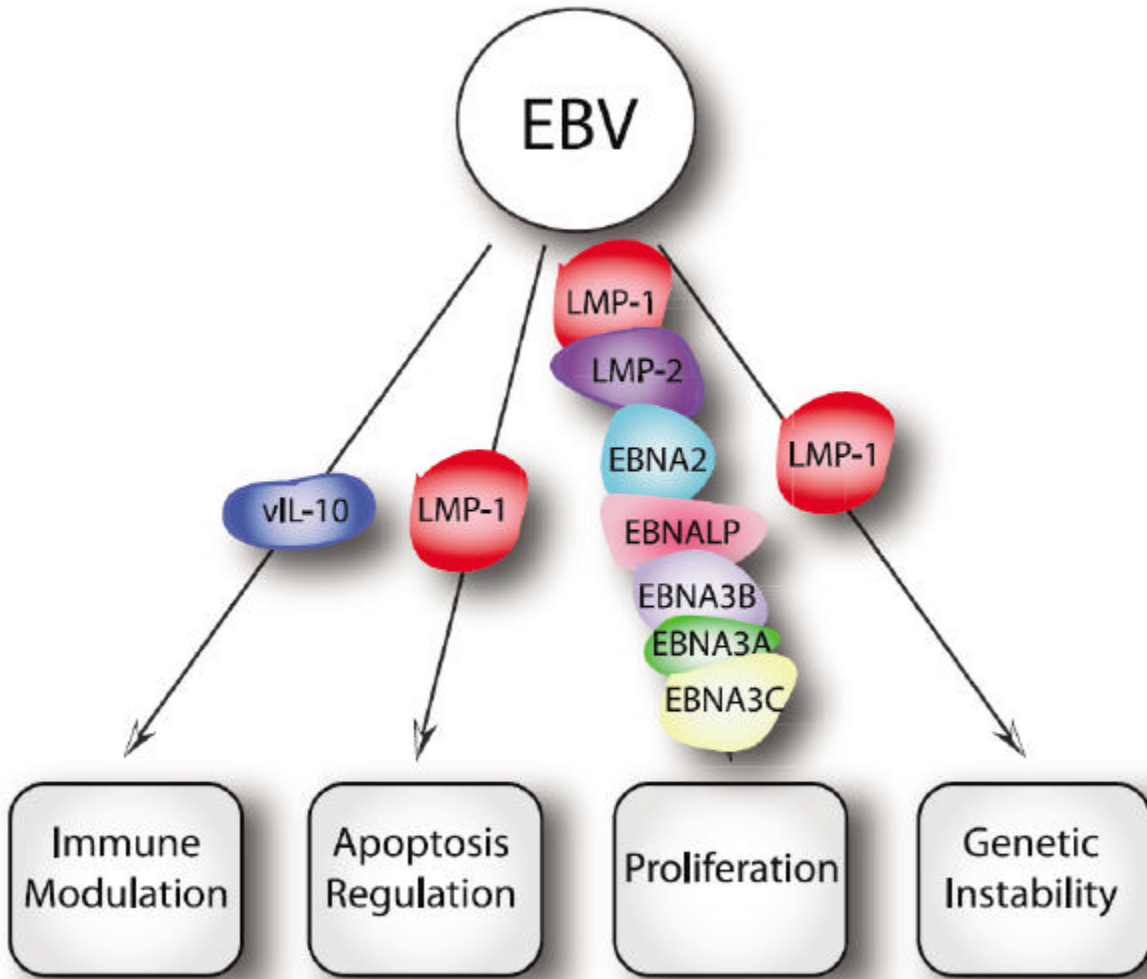


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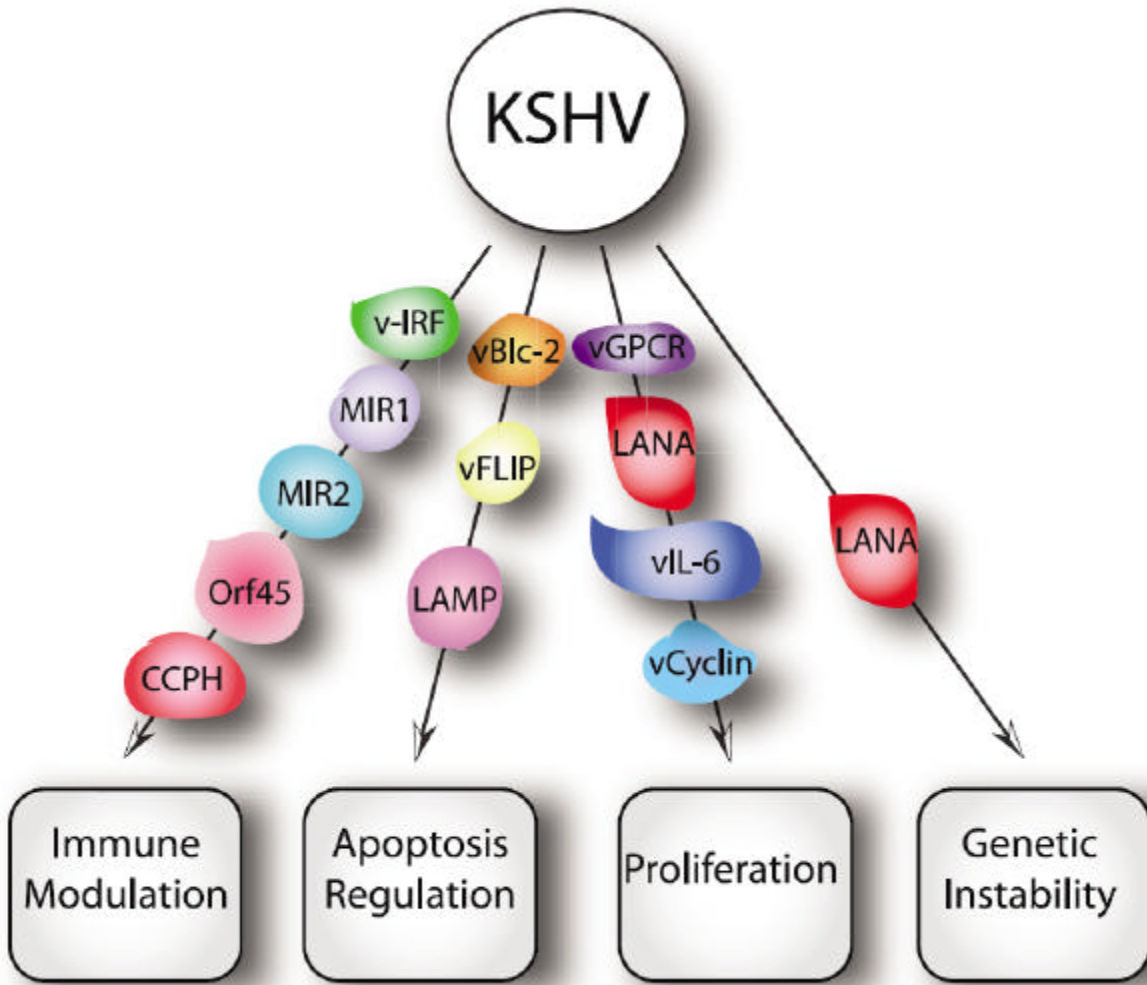


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