



HAL
open science

Viruses Associated with Human Cancer

Margaret E. Mclaughlin-Drubin, Karl Munger

► **To cite this version:**

Margaret E. Mclaughlin-Drubin, Karl Munger. Viruses Associated with Human Cancer. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, 2008, 1782 (3), pp.127. 10.1016/j.bbadis.2007.12.005 . hal-00562813

HAL Id: hal-00562813

<https://hal.science/hal-00562813>

Submitted on 4 Feb 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Accepted Manuscript

Viruses Associated with Human Cancer

Margaret E. McLaughlin-Drubin, Karl Munger

PII: S0925-4439(07)00238-4
DOI: doi: [10.1016/j.bbadis.2007.12.005](https://doi.org/10.1016/j.bbadis.2007.12.005)
Reference: BBADIS 62775

To appear in: *BBA - Molecular Basis of Disease*

Received date: 5 November 2007
Revised date: 13 December 2007
Accepted date: 18 December 2007



Please cite this article as: Margaret E. McLaughlin-Drubin, Karl Munger, Viruses Associated with Human Cancer, *BBA - Molecular Basis of Disease* (2007), doi: [10.1016/j.bbadis.2007.12.005](https://doi.org/10.1016/j.bbadis.2007.12.005)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

1 **Viruses Associated with Human Cancer**

2
3
4 Margaret E. McLaughlin-Drubin and Karl Munger

5
6
7 The Channing Laboratory, Brigham and Women's Hospital and
8 Department of Medicine, Harvard Medical School, Boston MA 02115
9

10
11
12 Address for correspondence:

13
14 Margaret E. McLaughlin-Drubin or Karl Munger

15 Brigham and Women's Hospital

16 Channing Laboratories, 8th Floor

17 181 Longwood Avenue

18 Boston, MA 02115

19 Phone (617) 525-4282

20 Fax (617) 525-4283

21 E-mail: mdrubin@rics.bwh.harvard.edu or kmunger@rics.bwh.harvard.edu
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)
26

1	Table of Contents
2	Abstract
3	1. Introduction
4	2. Historic Context
5	3. General Aspects of Viral Carcinogenesis
6	4. Criteria for Defining an Etiologic Role for Viruses in Cancer
7	5. Human Oncogenic Viruses
8	5.1. RNA Tumor Viruses
9	5.1.1 Human T-Cell Leukemia Virus (HTLV-1)
10	5.1.2 Hepatitis C Virus (HCV)
11	5.2. DNA Tumor Viruses
12	5.2.1. Human Papillomavirus (HPV)
13	5.2.2 Hepatitis B Virus (HBV)
14	5.2.3. Epstein-Barr Virus (EBV)
15	5.2.4 Kaposi's Sarcoma-Associated Herpesvirus (KSHV)/Human Herpes Virus 8
16	(HHV8)
17	6. Viruses Implicated in Human Cancers
18	6.1. Polyomaviruses
19	6.2. Adenoviruses
20	6.3. Human Endogenous Retroviruses (HERVs)
21	6.4. Human Mammary Tumor Virus (HMTV)/Pogo Virus
22	6.5. Xenotropic Murine Leukemia Virus-Related Virus (XMRV)
23	6.6 Torque teno virus (TTV)
24	7. Concluding Remarks/Perspectives
25	8. References
26	
27	

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 19th 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].

17

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- κ 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^{INK4A} [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- κ 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- κ 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[†])
3 [288-291]. More than one-third of HBV-integrates in HBV related HCC encode functional MHBs[†]
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[†] 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[†] 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 γ 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_s -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- κ B, Jun, and p38 in LMP1-expressing epithelial and B cells [305-307]. Through
10 NF- κ 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- κ 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 γ -herpesvirus subfamily and, like other γ -herpesviruses, establishes lifelong
14 latency in B cells. KSHV is associated with all forms of KS, primary effusion lymphomas
15 (PELs), and multicentric Castleman's 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- κ 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].
9

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

11 **Acknowledgments**

12 We apologize to those authors whose important contributions could not be appropriately
13 discussed and cited due to space limitations. We thank E. Cahir-McFarland and M. Imperiale for
14 critical comments on parts of this manuscript. The research on viral oncology in the authors'
15 laboratory is supported by PHS grants CA066980, CA081135; M M-D is supported by PF-07-
16 072-01-MBC from the American Cancer Society. This article is dedicated to the memory of
17 Konrad Lerch.

18

19

20

1 **References**

- 2
- 3 [1] D.M. Parkin, F. Bray, J. Ferlay and P. Pisani, Global cancer statistics, 2002, *CA Cancer*
4 *J Clin* 55 (2005) 74-108.
- 5 [2] H. zur Hausen, Viruses in human cancers, *Current Science* 81 (2001) 523-27.
- 6 [3] D.M. Parkin, The global health burden of infection-associated cancers in the year 2002,
7 *Int J Cancer* 118 (2006) 3030-44.
- 8 [4] J. M'Fadyan and F. Hobday, Note on the experimental "transmission of warts in the
9 dog", *J Comp Pathol Ther* 11 (1898) 341-43.
- 10 [5] G. Ciuffo, Innesto positivo con filtrato di verruca volgare, *Giorn Ital Mal Venereol* 48
11 (1907) 12-17.
- 12 [6] V. Ellermann and O. Bang, Experimentelle Leukämie bei Hühnern, *Centralbt. f. Bakt.*
13 *Abt. I (orig)* 46 (1908) 595-609.
- 14 [7] P. Rous, Transmission of a malignant new growth by means of a cell-free filtrate, *J Am.*
15 *Med. Assoc.* 56 (1911) 198.
- 16 [8] L. Gross, Susceptibility of newborn mice of an otherwise apparently 'resistant' strain to
17 inoculation with leukemia, *Proc Soc Exp Biol Med* 73 (1950) 246-248.
- 18 [9] S.E. Stewart, B.E. Eddy and N. Borgese, Neoplasms in mice inoculated with a tumor
19 agent carried in tissue culture, *J Natl Cancer Inst* 20 (1958) 1223-1243.
- 20 [10] M.A. Epstein, B.G. Achong and Y.M. Barr, Virus particles in cultured lymphoblasts from
21 Burkitt's lymphoma, *Lancet* i (1964).
- 22 [11] D.S. Dane, C.H. Cameron and M. Briggs, Virus-like particles in serum of patients with
23 Australia-antigen-associated hepatitis, *Lancet* 1 (1970) 695-8.

- 1 [12] M. Durst, L. Gissmann, H. Ikenberg and H. zur Hausen, A papillomavirus DNA from a
2 cervical carcinoma and its prevalence in cancer biopsy samples from different
3 geographic regions, Proc Natl Acad Sci U S A 80 (1983) 3812-5.
- 4 [13] M. Boshart, L. Gissmann, H. Ikenberg, A. Kleinheinz, W. Scheurlen and H. zur Hausen,
5 A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell
6 lines derived from cervical cancer, Embo J 3 (1984) 1151-7.
- 7 [14] R.P. Beasley, L.Y. Hwang, C.C. Lin and C.S. Chien, Hepatocellular carcinoma and
8 hepatitis B virus. A prospective study of 22 707 men in Taiwan, Lancet 2 (1981) 1129-
9 33.
- 10 [15] B.J. Poiesz, F.W. Ruscetti, A.F. Gazdar, P.A. Bunn, J.D. Minna and R.C. Gallo,
11 Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes
12 of a patient with cutaneous T-cell lymphoma, Proc Natl Acad Sci U S A 77 (1980) 7415-
13 9.
- 14 [16] M. Yoshida, I. Miyoshi and Y. Hinuma, Isolation and characterization of retrovirus from
15 cell lines of human adult T-cell leukemia and its implication in the disease, Proc Natl
16 Acad Sci U S A 79 (1982) 2031-5.
- 17 [17] Q.L. Choo, G. Kuo, A.J. Weiner, L.R. Overby, D.W. Bradley and M. Houghton, Isolation
18 of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome,
19 Science 244 (1989) 359-62.
- 20 [18] Y. Chang, E. Cesarman, M.S. Pessin, F. Lee, J. Culpepper, D.M. Knowles and P.S.
21 Moore, Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's
22 sarcoma, Science 266 (1994) 1865-9.
- 23 [19] S.M. Cohen. in (Parsonnet, J., ed.) Microbes and Malignancy: Infection as a Cause of
24 Human Cancers, Oxford University Press, Oxford, UK 1999, pp. 89-106.
- 25 [20] R. Koch. in Verhandlungen des X Internationalen Medicinischen Congresses, Vol. 1,
26 pp. 35-47, Berlin 1890.

- 1 [21] A.S. Evans and N.E. Mueller, Viruses and cancer. Causal associations, *Ann Epidemiol* 1
2 (1990) 71-92.
- 3 [22] A.B. Hill, The Environment and Disease: Association or Causation?, *Proc R Soc Med* 58
4 (1965) 295-300.
- 5 [23] A.B. Hill and I.D. Hill, *Bradford Hill's Principles of Medical Statistics*, 12th ed., Edward
6 Arnold, London, UK, 1991.
- 7 [24] C.Z. Giam and K.T. Jeang, HTLV-1 Tax and adult T-cell leukemia, *Front Biosci* 12
8 (2007) 1496-507.
- 9 [25] H. zur Hausen, Papillomavirus infections--a major cause of human cancers, *Biochim*
10 *Biophys Acta* 1288 (1996) F55-78.
- 11 [26] H. zur Hausen, Immortalization of human cells and their malignant conversion by high
12 risk human papillomavirus genotypes, *Semin Cancer Biol* 9 (1999) 405-11.
- 13 [27] K. Munger, A. Baldwin, K.M. Edwards, H. Hayakawa, C.L. Nguyen, M. Owens, M. Grace
14 and K. Huh, Mechanisms of human papillomavirus-induced oncogenesis, *J Virol* 78
15 (2004) 11451-60.
- 16 [28] M. Schiffman, P.E. Castle, J. Jeronimo, A.C. Rodriguez and S. Wacholder, Human
17 papillomavirus and cervical cancer, *Lancet* 370 (2007) 890-907.
- 18 [29] J. Nicholas, Human herpesvirus 8-encoded proteins with potential roles in virus-
19 associated neoplasia, *Front Biosci* 12 (2007) 265-81.
- 20 [30] G. Cathomas, Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8
21 (HHV-8) as a tumour virus, *Herpes* 10 (2003) 72-7.
- 22 [31] J.S. Pagano, Epstein-Barr virus: the first human tumor virus and its role in cancer, *Proc*
23 *Assoc Am Physicians* 111 (1999) 573-80.
- 24 [32] Q. Tao, L.S. Young, C.B. Woodman and P.G. Murray, Epstein-Barr virus (EBV) and its
25 associated human cancers--genetics, epigenetics, pathobiology and novel therapeutics,
26 *Front Biosci* 11 (2006) 2672-713.

- 1 [33] E. Klein, L.L. Kis and G. Klein, Epstein-Barr virus infection in humans: from harmless to
2 life endangering virus-lymphocyte interactions, *Oncogene* 26 (2007) 1297-305.
- 3 [34] D.Y. Jin, Molecular pathogenesis of hepatitis C virus-associated hepatocellular
4 carcinoma, *Front Biosci* 12 (2007) 222-33.
- 5 [35] M. Levrero, Viral hepatitis and liver cancer: the case of hepatitis C, *Oncogene* 25 (2006)
6 3834-47.
- 7 [36] N.H. Park, I.H. Song and Y.H. Chung, Chronic hepatitis B in hepatocarcinogenesis,
8 *Postgrad Med J* 82 (2006) 507-15.
- 9 [37] D. Kremsdorf, P. Soussan, P. Paterlini-Brechot and C. Brechot, Hepatitis B virus-related
10 hepatocellular carcinoma: paradigms for viral-related human carcinogenesis, *Oncogene*
11 25 (2006) 3823-33.
- 12 [38] A.T. Lee and C.G. Lee, Oncogenesis and transforming viruses: the hepatitis B virus and
13 hepatocellularcarcinoma--the etiopathogenic link, *Front Biosci* 12 (2007) 234-45.
- 14 [39] B.H. Sweet and M.R. Hilleman, The vacuolating virus, S.V. 40, *Proc Soc Exp Biol Med*
15 105 (1960) 420-7.
- 16 [40] S.D. Gardner, A.M. Field, D.V. Coleman and B. Hulme, New human papovavirus (B.K.)
17 isolated from urine after renal transplantation, *Lancet* 1 (1971) 1253-7.
- 18 [41] M.J. Imperiale, Oncogenic transformation by the human polyomaviruses, *Oncogene* 20
19 (2001) 7917-23.
- 20 [42] B.L. Padgett, D.L. Walker, G.M. ZuRhein, R.J. Eckroade and B.H. Dessel, Cultivation of
21 papova-like virus from human brain with progressive multifocal leucoencephalopathy,
22 *Lancet* 1 (1971) 1257-60.
- 23 [43] N. Bannert and R. Kurth, Retroelements and the human genome: new perspectives on
24 an old relation, *Proc Natl Acad Sci U S A* 101 Suppl 2 (2004) 14572-9.
- 25 [44] R. Gifford and M. Tristem, The evolution, distribution and diversity of endogenous
26 retroviruses, *Virus Genes* 26 (2003) 291-315.

- 1 [45] J.F. Holland and B.G.T. Pogo, Mouse mammary tumor virus-like infection and human
2 breast cancer, *Clinical Cancer Research* 10 (2004) 5647-5649.
- 3 [46] T. Nishizawa, H. Okamoto, K. Konishi, H. Yoshizawa, Y. Miyakawa and M. Mayumi, A
4 novel DNA virus (TTV) associated with elevated transaminase levels in posttransfusion
5 hepatitis of unknown etiology, *Biochem Biophys Res Commun* 241 (1997) 92-7.
- 6 [47] H.M. Temin and H. Rubin, Characteristics of an assay for Rous sarcoma virus and Rous
7 sarcoma cells in tissue culture, *Virology* 6 (1958) 669-88.
- 8 [48] R. Kurth, Oncogenes in retroviruses and cells, *Naturwissenschaften* 70 (1983) 439-50.
- 9 [49] R.A. Bradshaw and S. Prentis. *Oncogenes and growth factors*, Elsevier, Amsterdam
10 1987.
- 11 [50] H.E. Varmus, The molecular genetics of cellular oncogenes, *Annu Rev Genet* 18 (1984)
12 553-612.
- 13 [51] R.A. Weinberg, The action of oncogenes in the cytoplasm and nucleus, *Science* 230
14 (1985) 770-6.
- 15 [52] R.A. Weinberg and M. Wigler, *Oncogenes and the molecular origins of cancer*, Cold
16 Spring Harbor Press, Cold Spring, NY, 1989.
- 17 [53] L.F. Parada, C.J. Tabin, C. Shih and R.A. Weinberg, Human EJ bladder carcinoma
18 oncogene is homologue of Harvey sarcoma virus ras gene, *Nature* 297 (1982) 474-8.
- 19 [54] R. Nusse, A. van Ooyen, D. Cox, Y.K. Fung and H. Varmus, Mode of proviral activation
20 of a putative mammary oncogene (int-1) on mouse chromosome 15, *Nature* 307 (1984)
21 131-6.
- 22 [55] G. Peters, C. Kozak and C. Dickson, Mouse mammary tumor virus integration regions
23 int-1 and int-2 map on different mouse chromosomes, *Mol Cell Biol* 4 (1984) 375-8.
- 24 [56] H.T. Cuypers, G. Selten, W. Quint, M. Zijlstra, E.R. Maandag, W. Boelens, P. van
25 Wezenbeek, C. Melief and A. Berns, Murine leukemia virus-induced T-cell

- 1 lymphomagenesis: integration of proviruses in a distinct chromosomal region, *Cell* 37
2 (1984) 141-50.
- 3 [57] M. van Lohuizen, S. Verbeek, B. Scheijen, E. Wientjens, H. van der Gulden and A.
4 Berns, Identification of cooperating oncogenes in E mu-myc transgenic mice by provirus
5 tagging, *Cell* 65 (1991) 737-52.
- 6 [58] S.E. Bear, A. Bellacosa, P.A. Lazo, N.A. Jenkins, N.G. Copeland, C. Hanson, G. Levan
7 and P.N. Tsichlis, Provirus insertion in Tpl-1, an Ets-1-related oncogene, is associated
8 with tumor progression in Moloney murine leukemia virus-induced rat thymic
9 lymphomas, *Proc Natl Acad Sci U S A* 86 (1989) 7495-9.
- 10 [59] A. Makris, C. Patriotis, S.E. Bear and P.N. Tsichlis, Structure of a Moloney murine
11 leukemia virus-virus-like 30 recombinant: implications for transduction of the c-Ha-ras
12 proto-oncogene, *J Virol* 67 (1993) 1286-91.
- 13 [60] G.G. Hicks and M. Mowat, Integration of Friend murine leukemia virus into both alleles of
14 the p53 oncogene in an erythroleukemic cell line, *J Virol* 62 (1988) 4752-5.
- 15 [61] A. Gessian, R. Yanagihara, G. Franchini, R.M. Garruto, C.L. Jenkins, A.B. Ajdukiewicz,
16 R.C. Gallo and D.C. Gajdusek, Highly divergent molecular variants of human T-
17 lymphotropic virus type I from isolated populations in Papua New Guinea and the
18 Solomon Islands, *Proc Natl Acad Sci U S A* 88 (1991) 7694-8.
- 19 [62] F. Wong-Staal and R.C. Gallo, Human T-lymphotropic retroviruses, *Nature* 317 (1985)
20 395-403.
- 21 [63] F.A. Proietti, A.B. Carneiro-Proietti, B.C. Catalan-Soares and E.L. Murphy, Global
22 epidemiology of HTLV-I infection and associated diseases, *Oncogene* 24 (2005) 6058-
23 68.
- 24 [64] M. Matsuoka and K.T. Jeang, Human T-cell leukaemia virus type 1 (HTLV-1) infectivity
25 and cellular transformation, *Nat Rev Cancer* 7 (2007) 270-80.

- 1 [65] M. Matsuoka, Human T-cell leukemia virus type I and adult T-cell leukemia, *Oncogene*
2 22 (2003) 5131-40.
- 3 [66] M. Nerenberg, S.H. Hinrichs, R.K. Reynolds, G. Khoury and G. Jay, The tat gene of
4 human T-lymphotropic virus type 1 induces mesenchymal tumors in transgenic mice,
5 *Science* 237 (1987) 1324-9.
- 6 [67] R. Grassmann, C. Dengler, I. Muller-Fleckenstein, B. Fleckenstein, K. McGuire, M.C.
7 Dokhelar, J.G. Sodroski and W.A. Haseltine, Transformation to continuous growth of
8 primary human T lymphocytes by human T-cell leukemia virus type I X-region genes
9 transduced by a Herpesvirus saimiri vector, *Proc Natl Acad Sci U S A* 86 (1989) 3351-5.
- 10 [68] R. Grassmann, S. Berchtold, I. Radant, M. Alt, B. Fleckenstein, J.G. Sodroski, W.A.
11 Haseltine and U. Ramstedt, Role of human T-cell leukemia virus type 1 X region proteins
12 in immortalization of primary human lymphocytes in culture, *J Virol* 66 (1992) 4570-5.
- 13 [69] R. Pozzatti, J. Vogel and G. Jay, The human T-lymphotropic virus type I tax gene can
14 cooperate with the ras oncogene to induce neoplastic transformation of cells, *Mol Cell*
15 *Biol* 10 (1990) 413-7.
- 16 [70] A. Tanaka, C. Takahashi, S. Yamaoka, T. Nosaka, M. Maki and M. Hatanaka,
17 Oncogenic transformation by the tax gene of human T-cell leukemia virus type I in vitro,
18 *Proc Natl Acad Sci U S A* 87 (1990) 1071-5.
- 19 [71] M.R. Smith and W.C. Greene, Functional analyses of the type I human T-cell leukemia
20 virus tax gene product, *Trans Assoc Am Physicians* 104 (1991) 78-91.
- 21 [72] S. Yamaoka, T. Tobe and M. Hatanaka, Tax protein of human T-cell leukemia virus type
22 I is required for maintenance of the transformed phenotype, *Oncogene* 7 (1992) 433-7.
- 23 [73] O. Rosin, C. Koch, I. Schmitt, O.J. Semmes, K.T. Jeang and R. Grassmann, A human T-
24 cell leukemia virus Tax variant incapable of activating NF-kappaB retains its
25 immortalizing potential for primary T-lymphocytes, *J Biol Chem* 273 (1998) 6698-703.

- 1 [74] Z.L. Chu, J.A. DiDonato, J. Hawiger and D.W. Ballard, The tax oncoprotein of human T-
2 cell leukemia virus type 1 associates with and persistently activates IkappaB kinases
3 containing IKKalpha and IKKbeta, *J Biol Chem* 273 (1998) 15891-4.
- 4 [75] S.C. Sun and D.W. Ballard, Persistent activation of NF-kappaB by the tax transforming
5 protein of HTLV-1: hijacking cellular IkappaB kinases, *Oncogene* 18 (1999) 6948-58.
- 6 [76] S.A. Leachman, R.E. Tigelaar, M. Shlyankevich, M.D. Slade, M. Irwin, E. Chang, T.C.
7 Wu, W. Xiao, S. Pazhani, D. Zelterman and J.L. Brandsma, Granulocyte-macrophage
8 colony-stimulating factor priming plus papillomavirus E6 DNA vaccination: effects on
9 papilloma formation and regression in the cottontail rabbit papillomavirus--rabbit model,
10 *J Virol* 74 (2000) 8700-8.
- 11 [77] D.Y. Jin, V. Giordano, K.V. Kibler, H. Nakano and K.T. Jeang, Role of adapter function in
12 oncoprotein-mediated activation of NF-kappaB. Human T-cell leukemia virus type I Tax
13 interacts directly with IkappaB kinase gamma, *J Biol Chem* 274 (1999) 17402-5.
- 14 [78] H. Iha, K.V. Kibler, V.R. Yedavalli, J.M. Peloponese, K. Haller, A. Miyazato, T. Kasai and
15 K.T. Jeang, Segregation of NF-kappaB activation through NEMO/IKKgamma by Tax and
16 TNFalpha: implications for stimulus-specific interruption of oncogenic signaling,
17 *Oncogene* 22 (2003) 8912-23.
- 18 [79] D.X. Fu, Y.L. Kuo, B.Y. Liu, K.T. Jeang and C.Z. Giam, Human T-lymphotropic virus type
19 I tax activates I-kappa B kinase by inhibiting I-kappa B kinase-associated
20 serine/threonine protein phosphatase 2A, *J Biol Chem* 278 (2003) 1487-93.
- 21 [80] G. Xiao, A. Fong and S.C. Sun, Induction of p100 processing by NF-kappaB-inducing
22 kinase involves docking IkappaB kinase alpha (IKKalpha) to p100 and IKKalpha-
23 mediated phosphorylation, *J Biol Chem* 279 (2004) 30099-105.
- 24 [81] M. Uhlik, L. Good, G. Xiao, E.W. Harhaj, E. Zandi, M. Karin and S.C. Sun, NF-kappaB-
25 inducing kinase and IkappaB kinase participate in human T-cell leukemia virus I Tax-
26 mediated NF-kappaB activation, *J Biol Chem* 273 (1998) 21132-6.

- 1 [82] G. Xiao and S.C. Sun, Activation of IKKalpha and IKKbeta through their fusion with
2 HTLV-I tax protein, *Oncogene* 19 (2000) 5198-203.
- 3 [83] G. Xiao, E.W. Harhaj and S.C. Sun, Domain-specific interaction with the I kappa B
4 kinase (IKK)regulatory subunit IKK gamma is an essential step in tax-mediated
5 activation of IKK, *J Biol Chem* 275 (2000) 34060-7.
- 6 [84] S.C. Sun and S. Yamaoka, Activation of NF-kappaB by HTLV-I and implications for cell
7 transformation, *Oncogene* 24 (2005) 5952-64.
- 8 [85] K.T. Jeang, Functional activities of the human T-cell leukemia virus type I Tax
9 oncoprotein: cellular signaling through NF-kappa B, *Cytokine Growth Factor Rev* 12
10 (2001) 207-17.
- 11 [86] C. Alexandre, P. Charnay and B. Verrier, Transactivation of Krox-20 and Krox-24
12 promoters by the HTLV-1 Tax protein through common regulatory elements, *Oncogene*
13 6 (1991) 1851-7.
- 14 [87] C. Alexandre and B. Verrier, Four regulatory elements in the human c-fos promoter
15 mediate transactivation by HTLV-1 Tax protein, *Oncogene* 6 (1991) 543-51.
- 16 [88] M. Fujii, T. Niki, T. Mori, T. Matsuda, M. Matsui, N. Nomura and M. Seiki, HTLV-1 Tax
17 induces expression of various immediate early serum responsive genes, *Oncogene* 6
18 (1991) 1023-9.
- 19 [89] M. Fujii, P. Sassone-Corsi and I.M. Verma, c-fos promoter trans-activation by the tax1
20 protein of human T-cell leukemia virus type I, *Proc Natl Acad Sci U S A* 85 (1988) 8526-
21 30.
- 22 [90] K. Nagata, K. Ohtani, M. Nakamura and K. Sugamura, Activation of endogenous c-fos
23 proto-oncogene expression by human T-cell leukemia virus type I-encoded p40tax
24 protein in the human T-cell line, Jurkat, *J Virol* 63 (1989) 3220-6.

- 1 [91] L.J. Zhao and C.Z. Giam, Human T-cell lymphotropic virus type I (HTLV-I) transcriptional
2 activator, Tax, enhances CREB binding to HTLV-I 21-base-pair repeats by protein-
3 protein interaction, Proc Natl Acad Sci U S A 89 (1992) 7070-4.
- 4 [92] J.M. Cox, L.S. Sloan and A. Schepartz, Conformation of Tax-response elements in the
5 human T-cell leukemia virus type I promoter, Chem Biol 2 (1995) 819-26.
- 6 [93] A.A. Franklin, M.F. Kubik, M.N. Uittenbogaard, A. Brauweiler, P. Utaisincharoen, M.A.
7 Matthews, W.S. Dynan, J.P. Hoeffler and J.K. Nyborg, Transactivation by the human T-
8 cell leukemia virus Tax protein is mediated through enhanced binding of activating
9 transcription factor-2 (ATF-2) ATF-2 response and cAMP element-binding protein
10 (CREB), J Biol Chem 268 (1993) 21225-31.
- 11 [94] R.P. Kwok, M.E. Laurance, J.R. Lundblad, P.S. Goldman, H. Shih, L.M. Connor, S.J.
12 Marriott and R.H. Goodman, Control of cAMP-regulated enhancers by the viral
13 transactivator Tax through CREB and the co-activator CBP, Nature 380 (1996) 642-6.
- 14 [95] K. Iwai, N. Mori, M. Oie, N. Yamamoto and M. Fujii, Human T-cell leukemia virus type 1
15 tax protein activates transcription through AP-1 site by inducing DNA binding activity in T
16 cells, Virology 279 (2001) 38-46.
- 17 [96] J.M. Peloponese, Jr. and K.T. Jeang, Role for Akt/protein kinase B and activator protein-
18 1 in cellular proliferation induced by the human T-cell leukemia virus type 1 tax
19 oncoprotein, J Biol Chem 281 (2006) 8927-38.
- 20 [97] H.A. Giebler, J.E. Loring, K. van Orden, M.A. Colgin, J.E. Garrus, K.W. Escudero, A.
21 Brauweiler and J.K. Nyborg, Anchoring of CREB binding protein to the human T-cell
22 leukemia virus type 1 promoter: a molecular mechanism of Tax transactivation, Mol Cell
23 Biol 17 (1997) 5156-64.
- 24 [98] B.A. Lenzmeier, H.A. Giebler and J.K. Nyborg, Human T-cell leukemia virus type 1 Tax
25 requires direct access to DNA for recruitment of CREB binding protein to the viral
26 promoter, Mol Cell Biol 18 (1998) 721-31.

- 1 [99] F. Bex, M.J. Yin, A. Burny and R.B. Gaynor, Differential transcriptional activation by
2 human T-cell leukemia virus type 1 Tax mutants is mediated by distinct interactions with
3 CREB binding protein and p300, *Mol Cell Biol* 18 (1998) 2392-405.
- 4 [100] R. Harrod, Y.L. Kuo, Y. Tang, Y. Yao, A. Vassilev, Y. Nakatani and C.Z. Giam, p300 and
5 p300/cAMP-responsive element-binding protein associated factor interact with human T-
6 cell lymphotropic virus type-1 Tax in a multi-histone acetyltransferase/activator-enhancer
7 complex, *J Biol Chem* 275 (2000) 11852-7.
- 8 [101] K.E. Scoggin, A. Ulloa and J.K. Nyborg, The oncoprotein Tax binds the SRC-1-
9 interacting domain of CBP/p300 to mediate transcriptional activation, *Mol Cell Biol* 21
10 (2001) 5520-30.
- 11 [102] R. Harrod, Y. Tang, C. Nicot, H.S. Lu, A. Vassilev, Y. Nakatani and C.Z. Giam, An
12 exposed KID-like domain in human T-cell lymphotropic virus type 1 Tax is responsible
13 for the recruitment of coactivators CBP/p300, *Mol Cell Biol* 18 (1998) 5052-61.
- 14 [103] J.P. Yan, J.E. Garrus, H.A. Giebler, L.A. Stargell and J.K. Nyborg, Molecular interactions
15 between the coactivator CBP and the human T-cell leukemia virus Tax protein, *J Mol*
16 *Biol* 281 (1998) 395-400.
- 17 [104] I. Lemasson, M.R. Lewis, N. Polakowski, P. Hivin, M.H. Cavanagh, S. Thebault, B.
18 Barbeau, J.K. Nyborg and J.M. Mesnard, Human T-cell leukemia virus type 1 (HTLV-1)
19 bZIP protein interacts with the cellular transcription factor CREB to inhibit HTLV-1
20 transcription, *J Virol* 81 (2007) 1543-53.
- 21 [105] M. Okada and K.T. Jeang, Differential requirements for activation of integrated and
22 transiently transfected human T-cell leukemia virus type 1 long terminal repeat, *J Virol*
23 76 (2002) 12564-73.
- 24 [106] R.L. Reid, P.F. Lindholm, A. Mireskandari, J. Dittmer and J.N. Brady, Stabilization of
25 wild-type p53 in human T-lymphocytes transformed by HTLV-I, *Oncogene* 8 (1993)
26 3029-36.

- 1 [107] C.A. Pise-Masison, K.S. Choi, M. Radonovich, J. Dittmer, S.J. Kim and J.N. Brady,
2 Inhibition of p53 transactivation function by the human T-cell lymphotropic virus type 1
3 Tax protein, *J Virol* 72 (1998) 1165-70.
- 4 [108] T. Suzuki, T. Narita, M. Uchida-Toita and M. Yoshida, Down-regulation of the INK4
5 family of cyclin-dependent kinase inhibitors by tax protein of HTLV-1 through two distinct
6 mechanisms, *Virology* 259 (1999) 384-91.
- 7 [109] K.G. Low, L.F. Dorner, D.B. Fernando, J. Grossman, K.T. Jeang and M.J. Comb, Human
8 T-cell leukemia virus type 1 Tax releases cell cycle arrest induced by p16INK4a, *J Virol*
9 71 (1997) 1956-62.
- 10 [110] D.Y. Jin, F. Spencer and K.T. Jeang, Human T cell leukemia virus type 1 oncoprotein
11 Tax targets the human mitotic checkpoint protein MAD1, *Cell* 93 (1998) 81-91.
- 12 [111] Y. Iwanaga, T. Kasai, K. Kibler and K.T. Jeang, Characterization of regions in hsMAD1
13 needed for binding hsMAD2. A polymorphic change in an hsMAD1 leucine zipper affects
14 MAD1-MAD2 interaction and spindle checkpoint function, *J Biol Chem* 277 (2002)
15 31005-13.
- 16 [112] T. Kasai, Y. Iwanaga, H. Iha and K.T. Jeang, Prevalent loss of mitotic spindle checkpoint
17 in adult T-cell leukemia confers resistance to microtubule inhibitors, *J Biol Chem* 277
18 (2002) 5187-93.
- 19 [113] T. Suzuki, Y. Ohsugi, M. Uchida-Toita, T. Akiyama and M. Yoshida, Tax oncoprotein of
20 HTLV-1 binds to the human homologue of *Drosophila* discs large tumor suppressor
21 protein, hDLG, and perturbs its function in cell growth control, *Oncogene* 18 (1999)
22 5967-72.
- 23 [114] A. Hirata, M. Higuchi, A. Niinuma, M. Ohashi, M. Fukushi, M. Oie, T. Akiyama, Y.
24 Tanaka, F. Gejyo and M. Fujii, PDZ domain-binding motif of human T-cell leukemia virus
25 type 1 Tax oncoprotein augments the transforming activity in a rat fibroblast cell line,
26 *Virology* 318 (2004) 327-36.

- 1 [115] C. Tsubata, M. Higuchi, M. Takahashi, M. Oie, Y. Tanaka, F. Gejyo and M. Fujii, PDZ
2 domain-binding motif of human T-cell leukemia virus type 1 Tax oncoprotein is essential
3 for the interleukin 2 independent growth induction of a T-cell line, *Retrovirology* 2 (2005)
4 46.
- 5 [116] L. Wang, D.P. Dittmer, C.C. Tomlinson, F.D. Fakhari and B. Damania, Immortalization of
6 primary endothelial cells by the K1 protein of Kaposi's sarcoma-associated herpesvirus,
7 *Cancer Res* 66 (2006) 3658-66.
- 8 [117] S. Takeda, M. Maeda, S. Morikawa, Y. Taniguchi, J. Yasunaga, K. Nosaka, Y. Tanaka
9 and M. Matsuoka, Genetic and epigenetic inactivation of tax gene in adult T-cell
10 leukemia cells, *Int J Cancer* 109 (2004) 559-67.
- 11 [118] Y. Furukawa, R. Kubota, M. Tara, S. Izumo and M. Osame, Existence of escape mutant
12 in HTLV-I tax during the development of adult T-cell leukemia, *Blood* 97 (2001) 987-93.
- 13 [119] T. Koiwa, A. Hamano-Usami, T. Ishida, A. Okayama, K. Yamaguchi, S. Kamihira and T.
14 Watanabe, 5'-long terminal repeat-selective CpG methylation of latent human T-cell
15 leukemia virus type 1 provirus in vitro and in vivo, *J Virol* 76 (2002) 9389-97.
- 16 [120] Y. Taniguchi, K. Nosaka, J. Yasunaga, M. Maeda, N. Mueller, A. Okayama and M.
17 Matsuoka, Silencing of human T-cell leukemia virus type I gene transcription by
18 epigenetic mechanisms, *Retrovirology* 2 (2005) 64.
- 19 [121] Y.P. Ching, S.F. Chan, K.T. Jeang and D.Y. Jin, The retroviral oncoprotein Tax targets
20 the coiled-coil centrosomal protein TAX1BP2 to induce centrosome overduplication, *Nat*
21 *Cell Biol* 8 (2006) 717-24.
- 22 [122] J.M. Peloponese, Jr., K. Haller, A. Miyazato and K.T. Jeang, Abnormal centrosome
23 amplification in cells through the targeting of Ran-binding protein-1 by the human T cell
24 leukemia virus type-1 Tax oncoprotein, *Proc Natl Acad Sci U S A* 102 (2005) 18974-9.

- 1 [123] T. Nitta, M. Kanai, E. Sugihara, M. Tanaka, B. Sun, T. Nagasawa, S. Sonoda, H. Saya
2 and M. Miwa, Centrosome amplification in adult T-cell leukemia and human T-cell
3 leukemia virus type 1 Tax-induced human T cells, *Cancer Sci* 97 (2006) 836-41.
- 4 [124] S. Kamihira, S. Atogami, H. Sohda, S. Momita, K. Toryia, S. Ikeda, Y. Yamada and M.
5 Tomonaga, DNA aneuploidy of adult T-cell leukemia cells, *Leuk Res* 18 (1994) 79-84.
- 6 [125] B. Liu, M.H. Liang, Y.L. Kuo, W. Liao, I. Boros, T. Kleinberger, J. Blancato and C.Z.
7 Giam, Human T-lymphotropic virus type 1 oncoprotein tax promotes unscheduled
8 degradation of Pds1p/securin and Clb2p/cyclin B1 and causes chromosomal instability,
9 *Mol Cell Biol* 23 (2003) 5269-81.
- 10 [126] B. Liu, S. Hong, Z. Tang, H. Yu and C.Z. Giam, HTLV-I Tax directly binds the Cdc20-
11 associated anaphase-promoting complex and activates it ahead of schedule, *Proc Natl*
12 *Acad Sci U S A* 102 (2005) 63-8.
- 13 [127] Y.L. Kuo and C.Z. Giam, Activation of the anaphase promoting complex by HTLV-1 tax
14 leads to senescence, *Embo J* 25 (2006) 1741-52.
- 15 [128] S.V. Sheleg, J.M. Peloponese, Y.H. Chi, Y. Li, M. Eckhaus and K.T. Jeang, Evidence for
16 cooperative transforming activity of the human pituitary tumor transforming gene and
17 human T-cell leukemia virus type 1 Tax, *J Virol* 81 (2007) 7894-901.
- 18 [129] G. Gaudray, F. Gachon, J. Basbous, M. Biard-Piechaczyk, C. Devaux and J.M.
19 Mesnard, The complementary strand of the human T-cell leukemia virus type 1 RNA
20 genome encodes a bZIP transcription factor that down-regulates viral transcription, *J*
21 *Virol* 76 (2002) 12813-22.
- 22 [130] D. Larocca, L.A. Chao, M.H. Seto and T.K. Brunck, Human T-cell leukemia virus minus
23 strand transcription in infected T-cells, *Biochem Biophys Res Commun* 163 (1989) 1006-
24 13.

- 1 [131] Y. Satou, J. Yasunaga, M. Yoshida and M. Matsuoka, HTLV-I basic leucine zipper factor
2 gene mRNA supports proliferation of adult T cell leukemia cells, *Proc Natl Acad Sci U S*
3 *A* 103 (2006) 720-5.
- 4 [132] C.W. Shepard, L. Finelli and M.J. Alter, Global epidemiology of hepatitis C virus
5 infection, *Lancet Infect Dis* 5 (2005) 558-67.
- 6 [133] G.M. Lauer and B.D. Walker, Hepatitis C virus infection, *N Engl J Med* 345 (2001) 41-52.
- 7 [134] I. Saito, T. Miyamura, A. Ohbayashi, H. Harada, T. Katayama, S. Kikuchi, Y. Watanabe,
8 S. Koi, M. Onji, Y. Ohta and et al., Hepatitis C virus infection is associated with the
9 development of hepatocellular carcinoma, *Proc Natl Acad Sci U S A* 87 (1990) 6547-9.
- 10 [135] M.J. Alter, Epidemiology of hepatitis C in the West, *Semin Liver Dis* 15 (1995) 5-14.
- 11 [136] T. Poynard, M.F. Yuen, V. Ratziu and C.L. Lai, Viral hepatitis C, *Lancet* 362 (2003)
12 2095-100.
- 13 [137] J.M. Pawlotsky, Pathophysiology of hepatitis C virus infection and related liver disease,
14 *Trends Microbiol* 12 (2004) 96-102.
- 15 [138] B.D. Lindenbach and C.M. Rice, Unravelling hepatitis C virus replication from genome to
16 function, *Nature* 436 (2005) 933-8.
- 17 [139] M. Gale, Jr. and E.M. Foy, Evasion of intracellular host defence by hepatitis C virus,
18 *Nature* 436 (2005) 939-45.
- 19 [140] D.G. Bowen and C.M. Walker, Adaptive immune responses in acute and chronic
20 hepatitis C virus infection, *Nature* 436 (2005) 946-52.
- 21 [141] B. Rehermann and M. Nascimbeni, Immunology of hepatitis B virus and hepatitis C virus
22 infection, *Nat Rev Immunol* 5 (2005) 215-29.
- 23 [142] S.F. Wieland and F.V. Chisari, Stealth and cunning: hepatitis B and hepatitis C viruses, *J*
24 *Viro* 79 (2005) 9369-80.
- 25 [143] C. Gremion and A. Cerny, Hepatitis C virus and the immune system: a concise review,
26 *Rev Med Virol* 15 (2005) 235-68.

- 1 [144] G.C. Sen and S.N. Sarkar, Transcriptional signaling by double-stranded RNA: role of
2 TLR3, *Cytokine Growth Factor Rev* 16 (2005) 1-14.
- 3 [145] E.J. Heathcote, Prevention of hepatitis C virus-related hepatocellular carcinoma,
4 *Gastroenterology* 127 (2004) S294-302.
- 5 [146] G. Fattovich, T. Stroffolini, I. Zagni and F. Donato, Hepatocellular carcinoma in cirrhosis:
6 incidence and risk factors, *Gastroenterology* 127 (2004) S35-50.
- 7 [147] T.J. Liang and T. Heller, Pathogenesis of hepatitis C-associated hepatocellular
8 carcinoma, *Gastroenterology* 127 (2004) S62-71.
- 9 [148] K. Moriya, H. Fujie, Y. Shintani, H. Yotsuyanagi, T. Tsutsumi, K. Ishibashi, Y. Matsuura,
10 S. Kimura, T. Miyamura and K. Koike, The core protein of hepatitis C virus induces
11 hepatocellular carcinoma in transgenic mice, *Nat Med* 4 (1998) 1065-7.
- 12 [149] H. Lerat, M. Honda, M.R. Beard, K. Loesch, J. Sun, Y. Yang, M. Okuda, R. Gosert, S.Y.
13 Xiao, S.A. Weinman and S.M. Lemon, Steatosis and liver cancer in transgenic mice
14 expressing the structural and nonstructural proteins of hepatitis C virus,
15 *Gastroenterology* 122 (2002) 352-65.
- 16 [150] A. Macdonald and M. Harris, Hepatitis C virus NS5A: tales of a promiscuous protein, *J*
17 *Gen Virol* 85 (2004) 2485-502.
- 18 [151] D.Y. Jin, H.L. Wang, Y. Zhou, A.C. Chun, K.V. Kibler, Y.D. Hou, H. Kung and K.T.
19 Jeang, Hepatitis C virus core protein-induced loss of LZIP function correlates with
20 cellular transformation, *Embo J* 19 (2000) 729-40.
- 21 [152] T. Munakata, M. Nakamura, Y. Liang, K. Li and S.M. Lemon, Down-regulation of the
22 retinoblastoma tumor suppressor by the hepatitis C virus NS5B RNA-dependent RNA
23 polymerase, *Proc Natl Acad Sci U S A* 102 (2005) 18159-64.
- 24 [153] I.S. Smirnova, N.D. Aksenov, E.V. Kashuba, P. Payakurel, V.V. Grabovetsky, A.D.
25 Zaberezhny, M.S. Vonsky, L. Buchinska, P. Biberfeld, J. Hinkula and M.G. Isaguliantis,

- 1 Hepatitis C virus core protein transforms murine fibroblasts by promoting genomic
2 instability, *Cell Oncol* 28 (2006) 177-90.
- 3 [154] B. Damania, DNA tumor viruses and human cancer, *Trends Microbiol* 15 (2007) 38-44.
- 4 [155] K. Munger and P.M. Howley, Human papillomavirus immortalization and transformation
5 functions, *Virus Res* 89 (2002) 213-28.
- 6 [156] A. Felsani, A.M. Mileo and M.G. Paggi, Retinoblastoma family proteins as key targets of
7 the small DNA virus oncoproteins, *Oncogene* 25 (2006) 5277-85.
- 8 [157] E. Harlow, P. Whyte, B.R. Franza, Jr. and C. Schley, Association of adenovirus early-
9 region 1A proteins with cellular polypeptides, *Mol Cell Biol* 6 (1986) 1579-89.
- 10 [158] P. Whyte, K.J. Buchkovich, J.M. Horowitz, S.H. Friend, M. Raybuck, R.A. Weinberg and
11 E. Harlow, Association between an oncogene and an anti-oncogene: the adenovirus
12 E1A proteins bind to the retinoblastoma gene product, *Nature* 334 (1988) 124-9.
- 13 [159] J.A. DeCaprio, J.W. Ludlow, J. Figge, J.Y. Shew, C.M. Huang, W.H. Lee, E. Marsilio, E.
14 Paucha and D.M. Livingston, SV40 large tumor antigen forms a specific complex with
15 the product of the retinoblastoma susceptibility gene, *Cell* 54 (1988) 275-83.
- 16 [160] N. Dyson, P.M. Howley, K. Munger and E. Harlow, The human papilloma virus-16 E7
17 oncoprotein is able to bind to the retinoblastoma gene product, *Science* 243 (1989) 934-
18 7.
- 19 [161] J.R. Nevins, E2F: a link between the Rb tumor suppressor protein and viral
20 oncoproteins, *Science* 258 (1992) 424-9.
- 21 [162] M.E. Ewen, J.W. Ludlow, E. Marsilio, J.A. DeCaprio, R.C. Millikan, S.H. Cheng, E.
22 Paucha and D.M. Livingston, An N-terminal transformation-governing sequence of SV40
23 large T antigen contributes to the binding of both p110Rb and a second cellular protein,
24 p120, *Cell* 58 (1989) 257-67.
- 25 [163] P. Whyte, N.M. Williamson and E. Harlow, Cellular targets for transformation by the
26 adenovirus E1A proteins, *Cell* 56 (1989) 67-75.

- 1 [164] K. Munger, B.A. Werness, N. Dyson, W.C. Phelps, E. Harlow and P.M. Howley,
2 Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor
3 suppressor gene product, *Embo J* 8 (1989) 4099-105.
- 4 [165] R. Reichel, I. Kovesdi and J.R. Nevins, Activation of a preexisting cellular factor as a
5 basis for adenovirus E1A-mediated transcription control, *Proc Natl Acad Sci U S A* 85
6 (1988) 387-90.
- 7 [166] S. Chellappan, V.B. Kraus, B. Kroger, K. Munger, P.M. Howley, W.C. Phelps and J.R.
8 Nevins, Adenovirus E1A, simian virus 40 tumor antigen, and human papillomavirus E7
9 protein share the capacity to disrupt the interaction between transcription factor E2F and
10 the retinoblastoma gene product, *Proc Natl Acad Sci U S A* 89 (1992) 4549-53.
- 11 [167] J.W. Ludlow, J.A. DeCaprio, C.M. Huang, W.H. Lee, E. Paucha and D.M. Livingston,
12 SV40 large T antigen binds preferentially to an underphosphorylated member of the
13 retinoblastoma susceptibility gene product family, *Cell* 56 (1989) 57-65.
- 14 [168] Y. Imai, Y. Matsushima, T. Sugimura and M. Terada, Purification and characterization of
15 human papillomavirus type 16 E7 protein with preferential binding capacity to the
16 underphosphorylated form of retinoblastoma gene product, *J Virol* 65 (1991) 4966-72.
- 17 [169] N. Dyson, P. Guida, K. Munger and E. Harlow, Homologous sequences in adenovirus
18 E1A and human papillomavirus E7 proteins mediate interaction with the same set of
19 cellular proteins, *J Virol* 66 (1992) 6893-902.
- 20 [170] S.N. Boyer, D.E. Wazer and V. Band, E7 protein of human papilloma virus-16 induces
21 degradation of retinoblastoma protein through the ubiquitin-proteasome pathway,
22 *Cancer Res* 56 (1996) 4620-4.
- 23 [171] D.L. Jones, D.A. Thompson and K. Munger, Destabilization of the RB tumor suppressor
24 protein and stabilization of p53 contribute to HPV type 16 E7-induced apoptosis,
25 *Virology* 239 (1997) 97-107.

- 1 [172] K. Huh, X. Zhou, H. Hayakawa, J.Y. Cho, T.A. Libermann, J. Jin, J.W. Harper and K.
2 Munger, Human papillomavirus type 16 E7 oncoprotein associates with the cullin 2
3 ubiquitin ligase complex, which contributes to degradation of the retinoblastoma tumor
4 suppressor, *J Virol* 81 (2007) 9737-47.
- 5 [173] D.P. Lane and L.V. Crawford, T antigen is bound to a host protein in SV40-transformed
6 cells, *Nature* 278 (1979) 261-3.
- 7 [174] D.I. Linzer and A.J. Levine, Characterization of a 54K dalton cellular SV40 tumor antigen
8 present in SV40-transformed cells and uninfected embryonal carcinoma cells, *Cell* 17
9 (1979) 43-52.
- 10 [175] P. Sarnow, Y.S. Ho, J. Williams and A.J. Levine, Adenovirus E1b-58kd tumor antigen
11 and SV40 large tumor antigen are physically associated with the same 54 kd cellular
12 protein in transformed cells, *Cell* 28 (1982) 387-94.
- 13 [176] B.A. Werness, A.J. Levine and P.M. Howley, Association of human papillomavirus types
14 16 and 18 E6 proteins with p53, *Science* 248 (1990) 76-9.
- 15 [177] C.A. Finlay, P.W. Hinds and A.J. Levine, The p53 proto-oncogene can act as a
16 suppressor of transformation, *Cell* 57 (1989) 1083-93.
- 17 [178] S.J. Baker, E.R. Fearon, J.M. Nigro, S.R. Hamilton, A.C. Preisinger, J.M. Jessup, P.
18 vanTuinen, D.H. Ledbetter, D.F. Barker, Y. Nakamura, R. White and B. Vogelstein,
19 Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas, *Science*
20 244 (1989) 217-21.
- 21 [179] P.R. Yew and A.J. Berk, Inhibition of p53 transactivation required for transformation by
22 adenovirus early 1B protein, *Nature* 357 (1992) 82-5.
- 23 [180] J.A. Mietz, T. Unger, J.M. Huibregtse and P.M. Howley, The transcriptional
24 transactivation function of wild-type p53 is inhibited by SV40 large T-antigen and by
25 HPV-16 E6 oncoprotein, *Embo J* 11 (1992) 5013-20.

- 1 [181] M.S. Lechner, D.H. Mack, A.B. Finicle, T. Crook, K.H. Vousden and L.A. Laimins,
2 Human papillomavirus E6 proteins bind p53 in vivo and abrogate p53-mediated
3 repression of transcription, *Embo J* 11 (1992) 3045-52.
- 4 [182] W.D. Funk, D.T. Pak, R.H. Karas, W.E. Wright and J.W. Shay, A transcriptionally active
5 DNA-binding site for human p53 protein complexes, *Mol Cell Biol* 12 (1992) 2866-71.
- 6 [183] S.E. Kern, J.A. Pietenpol, S. Thiagalingam, A. Seymour, K.W. Kinzler and B. Vogelstein,
7 Oncogenic forms of p53 inhibit p53-regulated gene expression, *Science* 256 (1992) 827-
8 30.
- 9 [184] D.P. Lane, *Cancer. p53, guardian of the genome*, *Nature* 358 (1992) 15-6.
- 10 [185] M. Oren, W. Maltzman and A.J. Levine, Post-translational regulation of the 54K cellular
11 tumor antigen in normal and transformed cells, *Mol Cell Biol* 1 (1981) 101-10.
- 12 [186] N.C. Reich, M. Oren and A.J. Levine, Two distinct mechanisms regulate the levels of a
13 cellular tumor antigen, p53, *Mol Cell Biol* 3 (1983) 2143-50.
- 14 [187] N.L. Hubbert, S.A. Sedman and J.T. Schiller, Human papillomavirus type 16 E6
15 increases the degradation rate of p53 in human keratinocytes, *J Virol* 66 (1992) 6237-41.
- 16 [188] M. Scheffner, K. Munger, J.C. Byrne and P.M. Howley, The state of the p53 and
17 retinoblastoma genes in human cervical carcinoma cell lines, *Proc Natl Acad Sci U S A*
18 88 (1991) 5523-7.
- 19 [189] M. Scheffner, B.A. Werness, J.M. Huibregtse, A.J. Levine and P.M. Howley, The E6
20 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the
21 degradation of p53, *Cell* 63 (1990) 1129-36.
- 22 [190] E.M. de Villiers, *Taxonomic Classification of Papillomaviruses*, *Papillomavirus Report* 12
23 (2001) 57-63.
- 24 [191] E.M. de Villiers, C. Fauquet, T.R. Broker, H.U. Bernard and H. zur Hausen,
25 *Classification of papillomaviruses*, *Virology* 324 (2004) 17-27.

- 1 [192] S. Jablonska, L. Fabjanska and I. Formas, On the viral etiology of epidermodysplasia
2 verruciformis, *Dermatologica* 132 (1966) 369-85.
- 3 [193] F. Pass, M. Reissig, K.V. Shah, M. Eisinger and G. Orth, Identification of an
4 immunologically distinct papillomavirus from lesions of epidermodysplasia verruciformis,
5 *J Natl Cancer Inst* 59 (1977) 1107-12.
- 6 [194] H. Pfister, F. Nurnberger, L. Gissmann and H. zur Hausen, Characterization of a human
7 papillomavirus from epidermodysplasia verruciformis lesions of a patient from Upper-
8 volta, *Int J Cancer* 27 (1981) 645-50.
- 9 [195] N. Ramoz, L.A. Rueda, B. Bouadjar, L.S. Montoya, G. Orth and M. Favre, Mutations in
10 two adjacent novel genes are associated with epidermodysplasia verruciformis, *Nat*
11 *Genet* 32 (2002) 579-81.
- 12 [196] G. Orth, S. Jablonska, M. Favre, O. Croissant, M. Jarzabek-Chorzelska and G. Rzeska,
13 Characterization of two types of human papillomaviruses in lesions of epidermodysplasia
14 verruciformis, *Proc Natl Acad Sci U S A* 75 (1978) 1537-41.
- 15 [197] V. Shamanin, M. Glover, C. Rausch, C. Proby, I.M. Leigh, H. zur Hausen and E.M. de
16 Villiers, Specific types of human papillomavirus found in benign proliferations and
17 carcinomas of the skin in immunosuppressed patients, *Cancer Res* 54 (1994) 4610-3.
- 18 [198] V. Shamanin, H. zur Hausen, D. Lavergne, C.M. Proby, I.M. Leigh, C. Neumann, H.
19 Hamm, M. Goos, U.F. Haustein, E.G. Jung, G. Plewig, H. Wolff and E.M. de Villiers,
20 Human papillomavirus infections in nonmelanoma skin cancers from renal transplant
21 recipients and nonimmunosuppressed patients, *J Natl Cancer Inst* 88 (1996) 802-11.
- 22 [199] I.L. Boxman, R.J. Berkhout, L.H. Mulder, M.C. Wolkers, J.N. Bouwes Bavinck, B.J.
23 Vermeer and J. ter Schegget, Detection of human papillomavirus DNA in plucked hairs
24 from renal transplant recipients and healthy volunteers, *J Invest Dermatol* 108 (1997)
25 712-5.

- 1 [200] I.L. Boxman, L.H. Mulder, A. Russell, J.N. Bouwes Bavinck, A. Green and J. Ter
2 Schegget, Human papillomavirus type 5 is commonly present in immunosuppressed and
3 immunocompetent individuals, *Br J Dermatol* 141 (1999) 246-9.
- 4 [201] B. Akgul, J.C. Cooke and A. Storey, HPV-associated skin disease, *J Pathol* 208 (2006)
5 165-75.
- 6 [202] S. Jackson, C. Harwood, M. Thomas, L. Banks and A. Storey, Role of Bak in UV-
7 induced apoptosis in skin cancer and abrogation by HPV E6 proteins, *Genes Dev* 14
8 (2000) 3065-73.
- 9 [203] T. Iftner, S. Bierfelder, Z. Csapo and H. Pfister, Involvement of human papillomavirus
10 type 8 genes E6 and E7 in transformation and replication, *J Virol* 62 (1988) 3655-61.
- 11 [204] S. Caldeira, I. Zehbe, R. Accardi, I. Malanchi, W. Dong, M. Giarre, E.M. de Villiers, R.
12 Filotico, P. Boukamp and M. Tommasino, The E6 and E7 proteins of the cutaneous
13 human papillomavirus type 38 display transforming properties, *J Virol* 77 (2003) 2195-
14 206.
- 15 [205] B. Akgul, R. Garcia-Escudero, L. Ghali, H.J. Pfister, P.G. Fuchs, H. Navsaria and A.
16 Storey, The E7 protein of cutaneous human papillomavirus type 8 causes invasion of
17 human keratinocytes into the dermis in organotypic cultures of skin, *Cancer Res* 65
18 (2005) 2216-23.
- 19 [206] B. Akgul, L. Ghali, D. Davies, H. Pfister, I.M. Leigh and A. Storey, HPV8 early genes
20 modulate differentiation and cell cycle of primary human adult keratinocytes, *Exp*
21 *Dermatol* 16 (2007) 590-9.
- 22 [207] I.D. Schaper, G.P. Marcuzzi, S.J. Weissenborn, H.U. Kasper, V. Dries, N. Smyth, P.
23 Fuchs and H. Pfister, Development of skin tumors in mice transgenic for early genes of
24 human papillomavirus type 8, *Cancer Res* 65 (2005) 1394-400.
- 25 [208] W. Dong, U. Kloz, R. Accardi, S. Caldeira, W.M. Tong, Z.Q. Wang, L. Jansen, M. Durst,
26 B.S. Sylla, L. Gissmann and M. Tommasino, Skin hyperproliferation and susceptibility to

- 1 chemical carcinogenesis in transgenic mice expressing E6 and E7 of human
2 papillomavirus type 38, *J Virol* 79 (2005) 14899-908.
- 3 [209] D.R. Lowy and P.M. Howley. in (Knipe, D.M. and Howley, P.M., eds.) *Fields' Virology*,
4 Lippincott Williams and Wilkins, New York 2001, pp. 2231-2264.
- 5 [210] D.I. Kutler, V.B. Wreesmann, A. Goberdhan, L. Ben-Porat, J. Satagopan, I. Ngai, A.G.
6 Huvos, P. Giampietro, O. Levran, K. Pujara, R. Diotti, D. Carlson, L.A. Hurn, A.D.
7 Auerbach and B. Singh, Human papillomavirus DNA and p53 polymorphisms in
8 squamous cell carcinomas from Fanconi anemia patients, *J Natl Cancer Inst* 95 (2003)
9 1718-21.
- 10 [211] N. Spardy, A. Duensing, D. Charles, N. Haines, T. Nakahara, P.F. Lambert and S.
11 Duensing, The human papillomavirus type 16 E7 oncoprotein activates the Fanconi
12 Anemia (FA) pathway and causes accelerated chromosomal instability in FA cells, *J*
13 *Virol* (2007).
- 14 [212] S. Jeon, B.L. Allen-Hoffmann and P.F. Lambert, Integration of human papillomavirus
15 type 16 into the human genome correlates with a selective growth advantage of cells, *J*
16 *Virol* 69 (1995) 2989-97.
- 17 [213] E.C. Goodwin and D. DiMaio, Repression of human papillomavirus oncogenes in HeLa
18 cervical carcinoma cells causes the orderly reactivation of dormant tumor suppressor
19 pathways, *Proc Natl Acad Sci U S A* 97 (2000) 12513-8.
- 20 [214] S.I. Wells, D.A. Francis, A.Y. Karpova, J.J. Dowhanick, J.D. Benson and P.M. Howley,
21 Papillomavirus E2 induces senescence in HPV-positive cells via pRB- and p21(CIP)-
22 dependent pathways, *Embo J* 19 (2000) 5762-71.
- 23 [215] P. Hawley-Nelson, K.H. Vousden, N.L. Hubbert, D.R. Lowy and J.T. Schiller, HPV16 E6
24 and E7 proteins cooperate to immortalize human foreskin keratinocytes, *Embo J* 8
25 (1989) 3905-10.

- 1 [216] K. Munger, W.C. Phelps, V. Bubb, P.M. Howley and R. Schlegel, The E6 and E7 genes
2 of the human papillomavirus type 16 together are necessary and sufficient for
3 transformation of primary human keratinocytes, *J Virol* 63 (1989) 4417-21.
- 4 [217] D.J. McCance, R. Kopan, E. Fuchs and L.A. Laimins, Human papillomavirus type 16
5 alters human epithelial cell differentiation in vitro, *Proc Natl Acad Sci U S A* 85 (1988)
6 7169-73.
- 7 [218] J.A. DiPaolo, C.D. Woodworth, N.C. Popescu, V. Notario and J. Doniger, Induction of
8 human cervical squamous cell carcinoma by sequential transfection with human
9 papillomavirus 16 DNA and viral Harvey ras, *Oncogene* 4 (1989) 395-9.
- 10 [219] M. Durst, D. Gallahan, G. Jay and J.S. Rhim, Glucocorticoid-enhanced neoplastic
11 transformation of human keratinocytes by human papillomavirus type 16 and an
12 activated ras oncogene, *Virology* 173 (1989) 767-71.
- 13 [220] X.F. Pei, J.M. Meck, D. Greenhalgh and R. Schlegel, Cotransfection of HPV-18 and v-
14 fos DNA induces tumorigenicity of primary human keratinocytes, *Virology* 196 (1993)
15 855-60.
- 16 [221] J.M. Arbeit, P.M. Howley and D. Hanahan, Chronic estrogen-induced cervical and
17 vaginal squamous carcinogenesis in human papillomavirus type 16 transgenic mice,
18 *Proc Natl Acad Sci U S A* 93 (1996) 2930-5.
- 19 [222] H. zur Hausen, Papillomaviruses and cancer: from basic studies to clinical application,
20 *Nat Rev Cancer* 2 (2002) 342-50.
- 21 [223] W.C. Phelps, C.L. Yee, K. Munger and P.M. Howley, The human papillomavirus type 16
22 E7 gene encodes transactivation and transformation functions similar to those of
23 adenovirus E1A, *Cell* 53 (1988) 539-47.
- 24 [224] A. Tanaka, T. Noda, H. Yajima, M. Hatanaka and Y. Ito, Identification of a transforming
25 gene of human papillomavirus type 16, *J Virol* 63 (1989) 1465-9.

- 1 [225] K.H. Vousden, J. Doniger, J.A. DiPaolo and D.R. Lowy, The E7 open reading frame of
2 human papillomavirus type 16 encodes a transforming gene, *Oncogene Res* 3 (1988)
3 167-75.
- 4 [226] S. Watanabe and K. Yoshiike, Transformation of rat 3Y1 cells by human papillomavirus
5 type-18 DNA, *Int J Cancer* 41 (1988) 896-900.
- 6 [227] G. Matlashewski, J. Schneider, L. Banks, N. Jones, A. Murray and L. Crawford, Human
7 papillomavirus type 16 DNA cooperates with activated ras in transforming primary cells,
8 *Embo J* 6 (1987) 1741-6.
- 9 [228] A. Storey and L. Banks, Human papillomavirus type 16 E6 gene cooperates with EJ-ras
10 to immortalize primary mouse cells, *Oncogene* 8 (1993) 919-24.
- 11 [229] M. Durst, R.T. Dzarlieva-Petrusevska, P. Boukamp, N.E. Fusenig and L. Gissmann,
12 Molecular and cytogenetic analysis of immortalized human primary keratinocytes
13 obtained after transfection with human papillomavirus type 16 DNA, *Oncogene* 1 (1987)
14 251-6.
- 15 [230] L. Pirisi, S. Yasumoto, M. Feller, J. Doniger and J.A. DiPaolo, Transformation of human
16 fibroblasts and keratinocytes with human papillomavirus type 16 DNA, *J Virol* 61 (1987)
17 1061-6.
- 18 [231] R. Schlegel, W.C. Phelps, Y.L. Zhang and M. Barbosa, Quantitative keratinocyte assay
19 detects two biological activities of human papillomavirus DNA and identifies viral types
20 associated with cervical carcinoma, *Embo J* 7 (1988) 3181-7.
- 21 [232] S. Watanabe, T. Kanda and K. Yoshiike, Human papillomavirus type 16 transformation
22 of primary human embryonic fibroblasts requires expression of open reading frames E6
23 and E7, *J Virol* 63 (1989) 965-9.
- 24 [233] C.D. Woodworth, P.E. Bowden, J. Doniger, L. Pirisi, W. Barnes, W.D. Lancaster and J.A.
25 DiPaolo, Characterization of normal human exocervical epithelial cells immortalized in
26 vitro by papillomavirus types 16 and 18 DNA, *Cancer Res* 48 (1988) 4620-8.

- 1 [234] A.E. White, E.M. Livanos and T.D. Tlsty, Differential disruption of genomic integrity and
2 cell cycle regulation in normal human fibroblasts by the HPV oncoproteins, *Genes Dev* 8
3 (1994) 666-77.
- 4 [235] S. Duensing and K. Munger, The human papillomavirus type 16 E6 and E7 oncoproteins
5 independently induce numerical and structural chromosome instability, *Cancer Res* 62
6 (2002) 7075-82.
- 7 [236] C.P. Crum, H. Ikenberg, R.M. Richart and L. Gissman, Human papillomavirus type 16
8 and early cervical neoplasia, *N Engl J Med* 310 (1984) 880-3.
- 9 [237] S. Duensing, L.Y. Lee, A. Duensing, J. Basile, S. Piboonniyom, S. Gonzalez, C.P. Crum
10 and K. Munger, The human papillomavirus type 16 E6 and E7 oncoproteins cooperate to
11 induce mitotic defects and genomic instability by uncoupling centrosome duplication
12 from the cell division cycle, *Proc Natl Acad Sci U S A* 97 (2000) 10002-7.
- 13 [238] S. Duensing, A. Duensing, C.P. Crum and K. Munger, Human papillomavirus type 16 E7
14 oncoprotein-induced abnormal centrosome synthesis is an early event in the evolving
15 malignant phenotype, *Cancer Res* 61 (2001) 2356-60.
- 16 [239] D. Ganem and A.M. Prince, Hepatitis B virus infection--natural history and clinical
17 consequences, *N Engl J Med* 350 (2004) 1118-29.
- 18 [240] J.H. Hoofnagle, G.M. Dusheiko, L.B. Seeff, E.A. Jones, J.G. Waggoner and Z.B. Bales,
19 Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis, *Ann*
20 *Intern Med* 94 (1981) 744-8.
- 21 [241] S. Wieland, R. Thimme, R.H. Purcell and F.V. Chisari, Genomic analysis of the host
22 response to hepatitis B virus infection, *Proc Natl Acad Sci U S A* 101 (2004) 6669-74.
- 23 [242] M.A. Feitelson, Hepatitis B virus in hepatocarcinogenesis, *J Cell Physiol* 181 (1999) 188-
24 202.
- 25 [243] A.S. Lok, Prevention of hepatitis B virus-related hepatocellular carcinoma,
26 *Gastroenterology* 127 (2004) S303-9.

- 1 [244] M. Singh and V. Kumar, Transgenic mouse models of hepatitis B virus-associated
2 hepatocellular carcinoma, *Rev Med Virol* 13 (2003) 243-53.
- 3 [245] C. Brechot, Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and
4 new paradigms, *Gastroenterology* 127 (2004) S56-61.
- 5 [246] H. Tanaka, Y. Iwasaki, K. Nouse, Y. Kobayashi, S. Nakamura, E. Matsumoto, N.
6 Toshikuni, T. Kaneyoshi, T. Ohsawa, K. Takaguchi, K. Fujio, T. Senoh, T. Ohnishi, K.
7 Sakaguchi and Y. Shiratori, Possible contribution of prior hepatitis B virus infection to the
8 development of hepatocellular carcinoma, *J Gastroenterol Hepatol* 20 (2005) 850-6.
- 9 [247] Y. Kajiya, K. Hamasaki, K. Nakata, S. Miyazoe, Y. Takeda, S. Higashi, K. Ohkubo, T.
10 Ichikawa, K. Nakao, Y. Kato and K. Eguchi, A long-term follow-up analysis of serial core
11 promoter and precore sequences in Japanese patients chronically infected by hepatitis B
12 virus, *Dig Dis Sci* 46 (2001) 509-15.
- 13 [248] C. Seeger and W.S. Mason, Hepatitis B virus biology, *Microbiol Mol Biol Rev* 64 (2000)
14 51-68.
- 15 [249] M.A. Feitelson and J. Lee, Hepatitis B virus integration, fragile sites, and
16 hepatocarcinogenesis, *Cancer Lett* 252 (2007) 157-70.
- 17 [250] C. Brechot, D. Gozuacik, Y. Murakami and P. Paterlini-Brechot, Molecular bases for the
18 development of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC), *Semin*
19 *Cancer Biol* 10 (2000) 211-31.
- 20 [251] M. Minami, Y. Daimon, K. Mori, H. Takashima, T. Nakajima, Y. Itoh and T. Okanoue,
21 Hepatitis B virus-related insertional mutagenesis in chronic hepatitis B patients as an
22 early drastic genetic change leading to hepatocarcinogenesis, *Oncogene* 24 (2005)
23 4340-8.
- 24 [252] M. Dandri, M.R. Burda, A. Burkle, D.M. Zuckerman, H. Will, C.E. Rogler, H. Greten and
25 J. Petersen, Increase in de novo HBV DNA integrations in response to oxidative DNA
26 damage or inhibition of poly(ADP-ribosyl)ation, *Hepatology* 35 (2002) 217-23.

- 1 [253] H.P. Wang, L. Zhang, M. Dandri and C.E. Rogler, Antisense downregulation of N-myc1
2 in woodchuck hepatoma cells reverses the malignant phenotype, *J Virol* 72 (1998) 2192-
3 8.
- 4 [254] H. Aoki, K. Kajino, Y. Arakawa and O. Hino, Molecular cloning of a rat chromosome
5 putative recombinogenic sequence homologous to the hepatitis B virus encapsidation
6 signal, *Proc Natl Acad Sci U S A* 93 (1996) 7300-4.
- 7 [255] O. Hino, K. Kajino, T. Umeda and Y. Arakawa, Understanding the hypercarcinogenic
8 state in chronic hepatitis: a clue to the prevention of human hepatocellular carcinoma, *J*
9 *Gastroenterol* 37 (2002) 883-7.
- 10 [256] I. Horikawa and J.C. Barrett, cis-Activation of the human telomerase gene (hTERT) by
11 the hepatitis B virus genome, *J Natl Cancer Inst* 93 (2001) 1171-3.
- 12 [257] M.J. Ferber, D.P. Montoya, C. Yu, I. Aderca, A. McGee, E.C. Thorland, D.M. Nagorney,
13 B.S. Gostout, L.J. Burgart, L. Boix, J. Bruix, B.J. McMahon, T.H. Cheung, T.K. Chung,
14 Y.F. Wong, D.I. Smith and L.R. Roberts, Integrations of the hepatitis B virus (HBV) and
15 human papillomavirus (HPV) into the human telomerase reverse transcriptase (hTERT)
16 gene in liver and cervical cancers, *Oncogene* 22 (2003) 3813-20.
- 17 [258] P. Paterlini-Brechot, K. Saigo, Y. Murakami, M. Chami, D. Gozuacik, C. Mugnier, D.
18 Lagorce and C. Brechot, Hepatitis B virus-related insertional mutagenesis occurs
19 frequently in human liver cancers and recurrently targets human telomerase gene,
20 *Oncogene* 22 (2003) 3911-6.
- 21 [259] Y. Murakami, K. Saigo, H. Takashima, M. Minami, T. Okanou, C. Brechot and P.
22 Paterlini-Brechot, Large scaled analysis of hepatitis B virus (HBV) DNA integration in
23 HBV related hepatocellular carcinomas, *Gut* 54 (2005) 1162-8.
- 24 [260] A. Tamori, Y. Yamanishi, S. Kawashima, M. Kanehisa, M. Enomoto, H. Tanaka, S.
25 Kubo, S. Shiomi and S. Nishiguchi, Alteration of gene expression in human

- 1 hepatocellular carcinoma with integrated hepatitis B virus DNA, Clin Cancer Res 11
2 (2005) 5821-6.
- 3 [261] P. Soussan, F. Garreau, H. Zylberberg, C. Ferray, C. Brechot and D. Kremsdorf, In vivo
4 expression of a new hepatitis B virus protein encoded by a spliced RNA, J Clin Invest
5 105 (2000) 55-60.
- 6 [262] J. Diao, R. Garces and C.D. Richardson, X protein of hepatitis B virus modulates
7 cytokine and growth factor related signal transduction pathways during the course of
8 viral infections and hepatocarcinogenesis, Cytokine Growth Factor Rev 12 (2001) 189-
9 205.
- 10 [263] M. Wollersheim, U. Debelka and P.H. Hofschneider, A transactivating function encoded
11 in the hepatitis B virus X gene is conserved in the integrated state, Oncogene 3 (1988)
12 545-52.
- 13 [264] P. Paterlini, K. Poussin, M. Kew, D. Franco and C. Brechot, Selective accumulation of
14 the X transcript of hepatitis B virus in patients negative for hepatitis B surface antigen
15 with hepatocellular carcinoma, Hepatology 21 (1995) 313-21.
- 16 [265] Y. Wei, J. Etienne, G. Fourel, L. Vitvitski-Trepo and M.A. Buendia, Hepadna virus
17 integration generates virus-cell cotranscripts carrying 3' truncated X genes in human and
18 woodchuck liver tumors, J Med Virol 45 (1995) 82-90.
- 19 [266] Q. Su, C.H. Schroder, W.J. Hofmann, G. Otto, R. Pichlmayr and P. Bannasch,
20 Expression of hepatitis B virus X protein in HBV-infected human livers and
21 hepatocellular carcinomas, Hepatology 27 (1998) 1109-20.
- 22 [267] H. Sirma, C. Giannini, K. Poussin, P. Paterlini, D. Kremsdorf and C. Brechot, Hepatitis B
23 virus X mutants, present in hepatocellular carcinoma tissue abrogate both the
24 antiproliferative and transactivation effects of HBx, Oncogene 18 (1999) 4848-59.
- 25 [268] Z. Peng, Y. Zhang, W. Gu, Z. Wang, D. Li, F. Zhang, G. Qiu and K. Xie, Integration of
26 the hepatitis B virus X fragment in hepatocellular carcinoma and its effects on the

- 1 expression of multiple molecules: a key to the cell cycle and apoptosis, *Int J Oncol* 26
2 (2005) 467-73.
- 3 [269] H.S. Chen, S. Kaneko, R. Girones, R.W. Anderson, W.E. Hornbuckle, B.C. Tennant, P.J.
4 Cote, J.L. Gerin, R.H. Purcell and R.H. Miller, The woodchuck hepatitis virus X gene is
5 important for establishment of virus infection in woodchucks, *J Virol* 67 (1993) 1218-26.
- 6 [270] F. Zoulim, J. Saputelli and C. Seeger, Woodchuck hepatitis virus X protein is required for
7 viral infection in vivo, *J Virol* 68 (1994) 2026-30.
- 8 [271] M. Melegari, S.K. Wolf and R.J. Schneider, Hepatitis B virus DNA replication is
9 coordinated by core protein serine phosphorylation and HBx expression, *J Virol* 79
10 (2005) 9810-20.
- 11 [272] H. Tang, L. Delgermaa, F. Huang, N. Oishi, L. Liu, F. He, L. Zhao and S. Murakami, The
12 transcriptional transactivation function of HBx protein is important for its augmentation
13 role in hepatitis B virus replication, *J Virol* 79 (2005) 5548-56.
- 14 [273] C. Brechot, V. Thiers, D. Kremsdorf, B. Nalpas, S. Pol and P. Paterlini-Brechot,
15 Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen:
16 clinically significant or purely "occult"?, *Hepatology* 34 (2001) 194-203.
- 17 [274] N.P. Klein, M.J. Bouchard, L.H. Wang, C. Kobarg and R.J. Schneider, Src kinases
18 involved in hepatitis B virus replication, *Embo J* 18 (1999) 5019-27.
- 19 [275] T.S. Yen, Hepadnaviral X Protein: Review of Recent Progress, *J Biomed Sci* 3 (1996) 20-
20 30.
- 21 [276] M.J. Bouchard and R.J. Schneider, The enigmatic X gene of hepatitis B virus, *J Virol* 78
22 (2004) 12725-34.
- 23 [277] P. Arbuthnot, A. Capovilla and M. Kew, Putative role of hepatitis B virus X protein in
24 hepatocarcinogenesis: effects on apoptosis, DNA repair, mitogen-activated protein
25 kinase and JAK/STAT pathways, *J Gastroenterol Hepatol* 15 (2000) 357-68.

- 1 [278] J.Y. Ahn, E.Y. Jung, H.J. Kwun, C.W. Lee, Y.C. Sung and K.L. Jang, Dual effects of
2 hepatitis B virus X protein on the regulation of cell-cycle control depending on the status
3 of cellular p53, *J Gen Virol* 83 (2002) 2765-72.
- 4 [279] R. Pang, E. Tse and R.T. Poon, Molecular pathways in hepatocellular carcinoma,
5 *Cancer Lett* 240 (2006) 157-69.
- 6 [280] J. Huang, J. Kwong, E.C. Sun and T.J. Liang, Proteasome complex as a potential
7 cellular target of hepatitis B virus X protein, *J Virol* 70 (1996) 5582-91.
- 8 [281] Z. Hu, Z. Zhang, E. Doo, O. Coux, A.L. Goldberg and T.J. Liang, Hepatitis B virus X
9 protein is both a substrate and a potential inhibitor of the proteasome complex, *J Virol* 73
10 (1999) 7231-40.
- 11 [282] Z. Zhang, N. Torii, A. Furusaka, N. Malayaman, Z. Hu and T.J. Liang, Structural and
12 functional characterization of interaction between hepatitis B virus X protein and the
13 proteasome complex, *J Biol Chem* 275 (2000) 15157-65.
- 14 [283] Z. Rahmani, K.W. Huh, R. Lasher and A. Siddiqui, Hepatitis B virus X protein colocalizes
15 to mitochondria with a human voltage-dependent anion channel, HVDAC3, and alters its
16 transmembrane potential, *J Virol* 74 (2000) 2840-6.
- 17 [284] K.W. Huh and A. Siddiqui, Characterization of the mitochondrial association of hepatitis
18 B virus X protein, HBx, *Mitochondrion* 1 (2002) 349-59.
- 19 [285] M. Chami, D. Ferrari, P. Nicotera, P. Paterlini-Brechot and R. Rizzuto, Caspase-
20 dependent alterations of Ca²⁺ signaling in the induction of apoptosis by hepatitis B virus
21 X protein, *J Biol Chem* 278 (2003) 31745-55.
- 22 [286] M.J. Bouchard, L.H. Wang and R.J. Schneider, Calcium signaling by HBx protein in
23 hepatitis B virus DNA replication, *Science* 294 (2001) 2376-8.
- 24 [287] M. Forgues, M.J. Difilippantonio, S.P. Linke, T. Ried, K. Nagashima, J. Feden, K.
25 Valerie, K. Fukasawa and X.W. Wang, Involvement of Crm1 in hepatitis B virus X

- 1 protein-induced aberrant centriole replication and abnormal mitotic spindles, *Mol Cell*
2 *Biol* 23 (2003) 5282-92.
- 3 [288] E. Hildt and P.H. Hofschneider, The PreS2 activators of the hepatitis B virus: activators
4 of tumour promoter pathways, *Recent Results Cancer Res* 154 (1998) 315-29.
- 5 [289] S. Murakami, Hepatitis B virus X protein: structure, function and biology, *Intervirology* 42
6 (1999) 81-99.
- 7 [290] A.S. Kekule, U. Lauer, M. Meyer, W.H. Caselmann, P.H. Hofschneider and R. Koshy,
8 The preS2/S region of integrated hepatitis B virus DNA encodes a transcriptional
9 transactivator, *Nature* 343 (1990) 457-61.
- 10 [291] E. Hildt, G. Saher, V. Bruss and P.H. Hofschneider, The hepatitis B virus large surface
11 protein (LHBs) is a transcriptional activator, *Virology* 225 (1996) 235-9.
- 12 [292] V. Schluter, M. Meyer, P.H. Hofschneider, R. Koshy and W.H. Caselmann, Integrated
13 hepatitis B virus X and 3' truncated preS/S sequences derived from human hepatomas
14 encode functionally active transactivators, *Oncogene* 9 (1994) 3335-44.
- 15 [293] S. Zhong, J.Y. Chan, W. Yeo, J.S. Tam and P.J. Johnson, Hepatitis B envelope protein
16 mutants in human hepatocellular carcinoma tissues, *J Viral Hepat* 6 (1999) 195-202.
- 17 [294] H.C. Wang, W. Huang, M.D. Lai and I.J. Su, Hepatitis B virus pre-S mutants,
18 endoplasmic reticulum stress and hepatocarcinogenesis, *Cancer Sci* 97 (2006) 683-8.
- 19 [295] E. Hildt, B. Munz, G. Saher, K. Reifenberg and P.H. Hofschneider, The PreS2 activator
20 MHBs(t) of hepatitis B virus activates c-raf-1/Erk2 signaling in transgenic mice, *Embo J*
21 21 (2002) 525-35.
- 22 [296] P. Soussan, R. Tuveri, B. Nalpas, F. Garreau, F. Zavala, A. Masson, S. Pol, C. Brechot
23 and D. Kremsdorf, The expression of hepatitis B spliced protein (HBSP) encoded by a
24 spliced hepatitis B virus RNA is associated with viral replication and liver fibrosis, *J*
25 *Hepatol* 38 (2003) 343-8.

- 1 [297] I.A.f.R.o. Cancer, Epstein-Barr virus and Kaposi sarcoma herpesvirus/human
2 herpesvirus 8, IARC Monograph 70 (1997).
- 3 [298] A.S. Evans and J.C. Niederman, Viral Infections of humans, Plenum Press, New York,
4 1989.
- 5 [299] S.H. Chan, Aetiology of nasopharyngeal carcinoma, Ann Acad Med Singapore 19 (1990)
6 201-7.
- 7 [300] L. Kruglyak, M.J. Daly, M.P. Reeve-Daly and E.S. Lander, Parametric and
8 nonparametric linkage analysis: a unified multipoint approach, Am J Hum Genet 58
9 (1996) 1347-63.
- 10 [301] D. Wang, D. Liebowitz and E. Kieff, An EBV membrane protein expressed in
11 immortalized lymphocytes transforms established rodent cells, Cell 43 (1985) 831-40.
- 12 [302] A. Rickinson and E. Kieff. in (Knipe, D.M. and Howley, P.M., eds.) Fields Virology,
13 Lippincott Williams and Wilkins, Philadelphia, PA 2001, pp. 2575-2627.
- 14 [303] G. Mosialos, M. Birkenbach, R. Yalamanchili, T. VanArsdale, C. Ware and E. Kieff, The
15 Epstein-Barr virus transforming protein LMP1 engages signaling proteins for the tumor
16 necrosis factor receptor family, Cell 80 (1995) 389-99.
- 17 [304] E. Kieff and A. Rickinson. in (Knipe, D.M. and Howley, P.M., eds.) Fields Virology,
18 Lippincott Williams and Wilkins, Philadelphia, PA 2001, pp. 2511-2573
- 19 .
- 20 [305] W.E. Miller, J.L. Cheshire, A.S. Baldwin, Jr. and N. Raab-Traub, The NPC derived C15
21 LMP1 protein confers enhanced activation of NF-kappa B and induction of the EGFR in
22 epithelial cells, Oncogene 16 (1998) 1869-77.
- 23 [306] A.G. Eliopoulos and L.S. Young, Activation of the cJun N-terminal kinase (JNK) pathway
24 by the Epstein-Barr virus-encoded latent membrane protein 1 (LMP1), Oncogene 16
25 (1998) 1731-42.

- 1 [307] A.G. Eliopoulos, N.J. Gallagher, S.M. Blake, C.W. Dawson and L.S. Young, Activation of
2 the p38 mitogen-activated protein kinase pathway by Epstein-Barr virus-encoded latent
3 membrane protein 1 coregulates interleukin-6 and interleukin-8 production, *J Biol Chem*
4 274 (1999) 16085-96.
- 5 [308] M. Rowe, M. Peng-Pilon, D.S. Huen, R. Hardy, D. Croom-Carter, E. Lundgren and A.B.
6 Rickinson, Upregulation of bcl-2 by the Epstein-Barr virus latent membrane protein
7 LMP1: a B-cell-specific response that is delayed relative to NF-kappa B activation and to
8 induction of cell surface markers, *J Virol* 68 (1994) 5602-12.
- 9 [309] L. Zhang and J.S. Pagano, Interferon regulatory factor 7 is induced by Epstein-Barr virus
10 latent membrane protein 1, *J Virol* 74 (2000) 1061-8.
- 11 [310] N. Wakisaka, S. Muroho, T. Yoshizaki, M. Furukawa and J.S. Pagano, Epstein-barr virus
12 latent membrane protein 1 induces and causes release of fibroblast growth factor-2,
13 *Cancer Res* 62 (2002) 6337-44.
- 14 [311] R.G. Caldwell, J.B. Wilson, S.J. Anderson and R. Longnecker, Epstein-Barr virus
15 LMP2A drives B cell development and survival in the absence of normal B cell receptor
16 signals, *Immunity* 9 (1998) 405-11.
- 17 [312] S.R. Grossman, E. Johannsen, X. Tong, R. Yalamanchili and E. Kieff, The Epstein-Barr
18 virus nuclear antigen 2 transactivator is directed to response elements by the J kappa
19 recombination signal binding protein, *Proc Natl Acad Sci U S A* 91 (1994) 7568-72.
- 20 [313] X. Tong, F. Wang, C.J. Thut and E. Kieff, The Epstein-Barr virus nuclear protein 2 acidic
21 domain can interact with TFIIB, TAF40, and RPA70 but not with TATA-binding protein, *J*
22 *Virol* 69 (1995) 585-8.
- 23 [314] J.I. Cohen and E. Kieff, An Epstein-Barr virus nuclear protein 2 domain essential for
24 transformation is a direct transcriptional activator, *J Virol* 65 (1991) 5880-5.

- 1 [315] B. Tomkinson and E. Kieff, Second-site homologous recombination in Epstein-Barr virus:
2 insertion of type 1 EBNA 3 genes in place of type 2 has no effect on in vitro infection, J
3 Virol 66 (1992) 780-9.
- 4 [316] E.S. Robertson, S. Grossman, E. Johannsen, C. Miller, J. Lin, B. Tomkinson and E.
5 Kieff, Epstein-Barr virus nuclear protein 3C modulates transcription through interaction
6 with the sequence-specific DNA-binding protein J kappa, J Virol 69 (1995) 3108-16.
- 7 [317] J.J. Russo, R.A. Bohenzky, M.C. Chien, J. Chen, M. Yan, D. Maddalena, J.P. Parry, D.
8 Peruzzi, I.S. Edelman, Y. Chang and P.S. Moore, Nucleotide sequence of the Kaposi
9 sarcoma-associated herpesvirus (HHV8), Proc Natl Acad Sci U S A 93 (1996) 14862-7.
- 10 [318] D.V. Ablashi, L.G. Chatlynne, J.E. Whitman, Jr. and E. Cesarman, Spectrum of Kaposi's
11 sarcoma-associated herpesvirus, or human herpesvirus 8, diseases, Clin Microbiol Rev
12 15 (2002) 439-64.
- 13 [319] T.F. Schulz, The pleiotropic effects of Kaposi's sarcoma herpesvirus, J Pathol 208
14 (2006) 187-98.
- 15 [320] O. Flore, S. Rafii, S. Ely, J.J. O'Leary, E.M. Hyjek and E. Cesarman, Transformation of
16 primary human endothelial cells by Kaposi's sarcoma-associated herpesvirus, Nature
17 394 (1998) 588-92.
- 18 [321] C. Lebbe, L. Blum, C. Pellet, G. Blanchard, O. Verola, P. Morel, O. Danne and F. Calvo,
19 Clinical and biological impact of antiretroviral therapy with protease inhibitors on HIV-
20 related Kaposi's sarcoma, Aids 12 (1998) F45-9.
- 21 [322] J. Gill, D. Bourboulia, J. Wilkinson, P. Hayes, A. Cope, A.G. Marcelin, V. Calvez, F.
22 Gotch, C. Boshoff and B. Gazzard, Prospective study of the effects of antiretroviral
23 therapy on Kaposi sarcoma--associated herpesvirus infection in patients with and
24 without Kaposi sarcoma, J Acquir Immune Defic Syndr 31 (2002) 384-90.

- 1 [323] Y. Aoki, E.S. Jaffe, Y. Chang, K. Jones, J. Teruya-Feldstein, P.S. Moore and G. Tosato,
2 Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-
3 encoded interleukin-6, *Blood* 93 (1999) 4034-43.
- 4 [324] J.T. Stine, C. Wood, M. Hill, A. Epp, C.J. Raport, V.L. Schweickart, Y. Endo, T. Sasaki,
5 G. Simmons, C. Boshoff, P. Clapham, Y. Chang, P. Moore, P.W. Gray and D. Chantry,
6 KSHV-encoded CC chemokine vMIP-III is a CCR4 agonist, stimulates angiogenesis, and
7 selectively chemoattracts TH2 cells, *Blood* 95 (2000) 1151-7.
- 8 [325] C. Boshoff, Y. Endo, P.D. Collins, Y. Takeuchi, J.D. Reeves, V.L. Schweickart, M.A.
9 Siani, T. Sasaki, T.J. Williams, P.W. Gray, P.S. Moore, Y. Chang and R.A. Weiss,
10 Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines, *Science* 278
11 (1997) 290-4.
- 12 [326] T.Y. Yang, S.C. Chen, M.W. Leach, D. Manfra, B. Homey, M. Wiekowski, L. Sullivan,
13 C.H. Jenh, S.K. Narula, S.W. Chensue and S.A. Lira, Transgenic expression of the
14 chemokine receptor encoded by human herpesvirus 8 induces an angioproliferative
15 disease resembling Kaposi's sarcoma, *J Exp Med* 191 (2000) 445-54.
- 16 [327] P.S. Moore and Y. Chang, Kaposi's sarcoma-associated herpesvirus immunoevasion
17 and tumorigenesis: two sides of the same coin?, *Annu Rev Microbiol* 57 (2003) 609-39.
- 18 [328] B. Damania, Oncogenic gamma-herpesviruses: comparison of viral proteins involved in
19 tumorigenesis, *Nat Rev Microbiol* 2 (2004) 656-68.
- 20 [329] E. Cesarman, E.A. Mesri and M.C. Gershengorn, Viral G protein-coupled receptor and
21 Kaposi's sarcoma: a model of paracrine neoplasia?, *J Exp Med* 191 (2000) 417-22.
- 22 [330] J. Nicholas, Human herpesvirus-8-encoded signalling ligands and receptors, *J Biomed*
23 *Sci* 10 (2003) 475-89.
- 24 [331] B.G. Bajaj, S.C. Verma, K. Lan, M.A. Cotter, Z.L. Woodman and E.S. Robertson, KSHV
25 encoded LANA upregulates Pim-1 and is a substrate for its kinase activity, *Virology* 351
26 (2006) 18-28.

- 1 [332] J. Friborg, Jr., W. Kong, M.O. Hottiger and G.J. Nabel, p53 inhibition by the LANA
2 protein of KSHV protects against cell death, *Nature* 402 (1999) 889-94.
- 3 [333] C. Swanton, D.J. Mann, B. Fleckenstein, F. Neipel, G. Peters and N. Jones, Herpes viral
4 cyclin/Cdk6 complexes evade inhibition by CDK inhibitor proteins, *Nature* 390 (1997)
5 184-7.
- 6 [334] D. Glykofrydes, H. Niphuis, E.M. Kuhn, B. Rosenwirth, J.L. Heeney, J. Bruder, G.
7 Niedobitek, I. Muller-Fleckenstein, B. Fleckenstein and A. Ensser, Herpesvirus saimiri
8 vFLIP provides an antiapoptotic function but is not essential for viral replication,
9 transformation, or pathogenicity, *J Virol* 74 (2000) 11919-27.
- 10 [335] M. Esteban, M.A. Garcia, E. Domingo-Gil, J. Arroyo, C. Nombela and C. Rivas, The
11 latency protein LANA2 from Kaposi's sarcoma-associated herpesvirus inhibits apoptosis
12 induced by dsRNA-activated protein kinase but not RNase L activation, *J Gen Virol* 84
13 (2003) 1463-70.
- 14 [336] C. McCormick and D. Ganem, The kaposin B protein of KSHV activates the p38/MK2
15 pathway and stabilizes cytokine mRNAs, *Science* 307 (2005) 739-41.
- 16 [337] H. Lee, R. Veazey, K. Williams, M. Li, J. Guo, F. Neipel, B. Fleckenstein, A. Lackner,
17 R.C. Desrosiers and J.U. Jung, Dereglulation of cell growth by the K1 gene of Kaposi's
18 sarcoma-associated herpesvirus, *Nat Med* 4 (1998) 435-40.
- 19 [338] O. Prakash, Z.Y. Tang, X. Peng, R. Coleman, J. Gill, G. Farr and F. Samaniego,
20 Tumorigenesis and aberrant signaling in transgenic mice expressing the human
21 herpesvirus-8 K1 gene, *J Natl Cancer Inst* 94 (2002) 926-35.
- 22 [339] T.V. Sharp, H.W. Wang, A. Koumi, D. Hollyman, Y. Endo, H. Ye, M.Q. Du and C.
23 Boshoff, K15 protein of Kaposi's sarcoma-associated herpesvirus is latently expressed
24 and binds to HAX-1, a protein with antiapoptotic function, *J Virol* 76 (2002) 802-16.
- 25 [340] B. Damania, Modulation of cell signaling pathways by Kaposi's sarcoma-associated
26 herpesvirus (KSHVHHV-8), *Cell Biochem Biophys* 40 (2004) 305-22.

- 1 [341] L. Gross, A filterable agent, recovered from Ak leukemic extracts, causing salivary gland
2 carcinomas in C3H mice, *Proc Soc Exp Biol Med* 83 (1953) 414-21.
- 3 [342] B.E. Eddy. in (Gard, C.H.S. and Meyers, K.F., eds.) *Virology Monographs*, Springer-
4 Verlag, New York 1969, pp. 1-114.
- 5 [343] L. Gross. *Oncogenic Viruses*, Pergamon Press, Oxford, New York, Toronto, Sydney,
6 Paris, Frankfurt 1983.
- 7 [344] T.L. Benjamin, Polyoma virus: old findings and new challenges, *Virology* 289 (2001)
8 167-73.
- 9 [345] H.H. Hirsch, W. Knowles, M. Dickenmann, J. Passweg, T. Klimkait, M.J. Mihatsch and J.
10 Steiger, Prospective study of polyomavirus type BK replication and nephropathy in renal-
11 transplant recipients, *N Engl J Med* 347 (2002) 488-96.
- 12 [346] P.S. Randhawa and A.J. Demetris, Nephropathy due to polyomavirus type BK, *N Engl J*
13 *Med* 342 (2000) 1361-3.
- 14 [347] J.R. Berger and I.J. Koralnik, Progressive multifocal leukoencephalopathy and
15 natalizumab--unforeseen consequences, *N Engl J Med* 353 (2005) 414-6.
- 16 [348] M. Safak and K. Khalili, An overview: Human polyomavirus JC virus and its associated
17 disorders, *J Neurovirol* 9 Suppl 1 (2003) 3-9.
- 18 [349] T. Allander, K. Andreasson, S. Gupta, A. Bjerkner, G. Bogdanovic, M.A. Persson, T.
19 Dalianis, T. Ramqvist and B. Andersson, Identification of a third human polyomavirus, *J*
20 *Virol* 81 (2007) 4130-6.
- 21 [350] A.M. Gaynor, M.D. Nissen, D.M. Whiley, I.M. Mackay, S.B. Lambert, G. Wu, D.C.
22 Brennan, G.A. Storch, T.P. Sloots and D. Wang, Identification of a novel polyomavirus
23 from patients with acute respiratory tract infections, *PLoS Pathog* 3 (2007) e64.
- 24 [351] M.K. White and K. Khalili, Polyomaviruses and human cancer: molecular mechanisms
25 underlying patterns of tumorigenesis, *Virology* 324 (2004) 1-16.

- 1 [352] K.V. Shah, SV40 and human cancer: a review of recent data, *Int J Cancer* 120 (2007)
2 215-23.
- 3 [353] D.L. Poulin and J.A. DeCaprio, Is there a role for SV40 in human cancer?, *J Clin Oncol*
4 24 (2006) 4356-65.
- 5 [354] G.L. Gallia, J. Gordon and K. Khalili, Tumor pathogenesis of human neurotropic JC virus
6 in the CNS, *J Neurovirol* 4 (1998) 175-81.
- 7 [355] D. Das, R.B. Shah and M.J. Imperiale, Detection and expression of human BK virus
8 sequences in neoplastic prostate tissues, *Oncogene* 23 (2004) 7031-46.
- 9 [356] M.B. Benko, B. Harrach and W.C. Russell. in (Van Regenmortel, M.H.V., Fauquet,
10 C.M., Bishop, D.H.L., Carsten, E.B., Estes, M.K., Lemon, S.M., Maniloff, J., Mayo, M.A.,
11 McGeoch, D.J., Pringle, R. and Wickner, R.B., eds.) *Virus Taxonomy. Seventh Report*
12 *of the International Committee on Taxonomy of Viruses*, Academic Press, New York
13 2000.
- 14 [357] C.T. Garnett, D. Erdman, W. Xu and L.R. Gooding, Prevalence and quantitation of
15 species C adenovirus DNA in human mucosal lymphocytes, *J Virol* 76 (2002) 10608-16.
- 16 [358] J. Horvath, L. Palkonyay and J. Weber, Group C adenovirus DNA sequences in human
17 lymphoid cells, *J Virol* 59 (1986) 189-92.
- 18 [359] J.K. Mackey, P.M. Rigden and M. Green, Do highly oncogenic group A human
19 adenoviruses cause human cancer? Analysis of human tumors for adenovirus 12
20 transforming DNA sequences, *Proc Natl Acad Sci U S A* 73 (1976) 4657-61.
- 21 [360] W.S. Wold, J.K. Mackey, P. Rigden and M. Green, Analysis of human cancer DNA's for
22 DNA sequence of human adenovirus serotypes 3, 7, 11, 14, 16, and 21 in group B1,
23 *Cancer Res* 39 (1979) 3479-84.
- 24 [361] M. Green, W.S. Wold, J.K. Mackey and P. Rigden, Analysis of human tonsil and cancer
25 DNAs and RNAs for DNA sequences of group C (serotypes 1, 2, 5, and 6) human
26 adenoviruses, *Proc Natl Acad Sci U S A* 76 (1979) 6606-10.

- 1 [362] K. Kosulin, C. Haberler, J.A. Hainfellner, G. Amann, S. Lang and T. Lion, Investigation of
2 adenovirus occurrence in pediatric tumor entities, *J Virol* 81 (2007) 7629-35.
- 3 [363] R.T. Javier, Adenovirus type 9 E4 open reading frame 1 encodes a transforming protein
4 required for the production of mammary tumors in rats, *J Virol* 68 (1994) 3917-24.
- 5 [364] M. Nevels, B. Tauber, T. Spruss, H. Wolf and T. Dobner, "Hit-and-run" transformation by
6 adenovirus oncogenes, *J Virol* 75 (2001) 3089-94.
- 7 [365] R. Lower, The pathogenic potential of endogenous retroviruses: facts and fantasies,
8 *Trends Microbiol* 7 (1999) 350-6.
- 9 [366] E.S. Lander, L.M. Linton, B. Birren, C. Nusbaum, M.C. Zody, J. Baldwin, K. Devon, K.
10 Dewar, M. Doyle, W. FitzHugh, R. Funke, D. Gage, K. Harris, A. Heaford, J. Howland, L.
11 Kann, J. Lehoczky, R. LeVine, P. McEwan, K. McKernan, J. Meldrim, J.P. Mesirov, C.
12 Miranda, W. Morris, J. Naylor, C. Raymond, M. Rosetti, R. Santos, A. Sheridan, C.
13 Sougnez, N. Stange-Thomann, N. Stojanovic, A. Subramanian, D. Wyman, J. Rogers, J.
14 Sulston, R. Ainscough, S. Beck, D. Bentley, J. Burton, C. Clee, N. Carter, A. Coulson, R.
15 Deadman, P. Deloukas, A. Dunham, I. Dunham, R. Durbin, L. French, D. Grafham, S.
16 Gregory, T. Hubbard, S. Humphray, A. Hunt, M. Jones, C. Lloyd, A. McMurray, L.
17 Matthews, S. Mercer, S. Milne, J.C. Mullikin, A. Mungall, R. Plumb, M. Ross, R.
18 Shownkeen, S. Sims, R.H. Waterston, R.K. Wilson, L.W. Hillier, J.D. McPherson, M.A.
19 Marra, E.R. Mardis, L.A. Fulton, A.T. Chinwalla, K.H. Pepin, W.R. Gish, S.L. Chissoe,
20 M.C. Wendl, K.D. Delehaunty, T.L. Miner, A. Delehaunty, J.B. Kramer, L.L. Cook, R.S.
21 Fulton, D.L. Johnson, P.J. Minx, S.W. Clifton, T. Hawkins, E. Branscomb, P. Predki, P.
22 Richardson, S. Wenning, T. Slezak, N. Doggett, J.F. Cheng, A. Olsen, S. Lucas, C.
23 Elkin, E. Uberbacher, M. Frazier, et al., Initial sequencing and analysis of the human
24 genome, *Nature* 409 (2001) 860-921.

- 1 [367] A.C. Andersson, A.C. Svensson, C. Rolny, G. Andersson and E. Larsson, Expression of
2 human endogenous retrovirus ERV3 (HERV-R) mRNA in normal and neoplastic tissues,
3 *Int J Oncol* 12 (1998) 309-13.
- 4 [368] M. Sauter, S. Schommer, E. Kremmer, K. Remberger, G. Dolken, I. Lemm, M. Buck, B.
5 Best, D. Neumann-Haefelin and N. Mueller-Lantzsch, Human endogenous retrovirus
6 K10: expression of Gag protein and detection of antibodies in patients with seminomas,
7 *J Virol* 69 (1995) 414-21.
- 8 [369] R. Lower, J. Lower, C. Tondera-Koch and R. Kurth, A general method for the
9 identification of transcribed retrovirus sequences (R-U5 PCR) reveals the expression of
10 the human endogenous retrovirus loci HERV-H and HERV-K in teratocarcinoma cells,
11 *Virology* 192 (1993) 501-11.
- 12 [370] A.M. Schulte, S. Lai, A. Kurtz, F. Czubayko, A.T. Riegel and A. Wellstein, Human
13 trophoblast and choriocarcinoma expression of the growth factor pleiotrophin attributable
14 to germ-line insertion of an endogenous retrovirus, *Proc Natl Acad Sci U S A* 93 (1996)
15 14759-64.
- 16 [371] T.K. Bera, T. Tsukamoto, D.K. Panda, T. Huang, R.C. Guzman, S.I. Hwang and S.
17 Nandi, Defective retrovirus insertion activates c-Ha-ras protooncogene in an MNU-
18 induced rat mammary carcinoma, *Biochem Biophys Res Commun* 248 (1998) 835-40.
- 19 [372] M. Sauter, K. Roemer, B. Best, M. Afting, S. Schommer, G. Seitz, M. Hartmann and N.
20 Mueller-Lantzsch, Specificity of antibodies directed against Env protein of human
21 endogenous retroviruses in patients with germ cell tumors, *Cancer Res* 56 (1996) 4362-
22 5.
- 23 [373] F. Wang-Johanning, J. Liu, K. Rycaj, M. Huang, K. Tsai, D.G. Rosen, D.T. Chen, D.W.
24 Lu, K.F. Barnhart and G.L. Johanning, Expression of multiple human endogenous
25 retrovirus surface envelope proteins in ovarian cancer, *Int J Cancer* 120 (2007) 81-90.

- 1 [374] T. Muster, A. Waltenberger, A. Grassauer, S. Hirschl, P. Caucig, I. Romirer, D. Fodinger,
2 H. Seppeler, O. Schanab, C. Magin-Lachmann, R. Lower, B. Jansen, H. Pehamberger
3 and K. Wolff, An endogenous retrovirus derived from human melanoma cells, *Cancer*
4 *Res* 63 (2003) 8735-41.
- 5 [375] K. Buscher, U. Trefzer, M. Hofmann, W. Sterry, R. Kurth and J. Denner, Expression of
6 human endogenous retrovirus K in melanomas and melanoma cell lines, *Cancer Res* 65
7 (2005) 4172-80.
- 8 [376] S.A. Tomlins, B. Laxman, S.M. Dhanasekaran, B.E. Helgeson, X. Cao, D.S. Morris, A.
9 Menon, X. Jing, Q. Cao, B. Han, J. Yu, L. Wang, J.E. Montie, M.A. Rubin, K.J. Pienta, D.
10 Roulston, R.B. Shah, S. Varambally, R. Mehra and A.M. Chinnaiyan, Distinct classes of
11 chromosomal rearrangements create oncogenic ETS gene fusions in prostate cancer,
12 *Nature* 448 (2007) 595-9.
- 13 [377] M. Denne, M. Sauter, V. Armbruester, J.D. Licht, K. Roemer and N. Mueller-Lantzsch,
14 Physical and functional interactions of human endogenous retrovirus proteins Np9 and
15 rec with the promyelocytic leukemia zinc finger protein, *J Virol* 81 (2007) 5607-16.
- 16 [378] J.J. Bittner, Some possible effects of nursing on the mammary gland tumor incidence in
17 mice, *Science* 84 (1936) 162.
- 18 [379] Y. Wang, J.F. Holland, I.J. Bleiweiss, S. Melana, X. Liu, I. Pelisson, A. Cantarella, K.
19 Stellrecht, S. Mani and B.G. Pogo, Detection of mammary tumor virus env gene-like
20 sequences in human breast cancer, *Cancer Res* 55 (1995) 5173-9.
- 21 [380] Y. Wang, I. Pelisson, S.M. Melana, J.F. Holland and B.G. Pogo, Detection of MMTV-like
22 LTR and LTR-env gene sequences in human breast cancer, *Int J Oncol* 18 (2001) 1041-
23 4.
- 24 [381] B. Liu, Y. Wang, S.M. Melana, I. Pelisson, V. Najfeld, J.F. Holland and B.G. Pogo,
25 Identification of a proviral structure in human breast cancer, *Cancer Res* 61 (2001) 1754-
26 9.

- 1 [382] S.M. Melana, I. Nepomnaschy, M. Sakalian, A. Abbott, J. Hasa, J.F. Holland and B.G.
2 Pogo, Characterization of viral particles isolated from primary cultures of human breast
3 cancer cells, *Cancer Res* 67 (2007) 8960-5.
- 4 [383] A. Bindra, S. Muradrasoli, R. Kisekka, H. Nordgren, F. Warnberg and J. Blomberg,
5 Search for DNA of exogenous mouse mammary tumor virus-related virus in human
6 breast cancer samples, *J Gen Virol* 88 (2007) 1806-9.
- 7 [384] T.H. Stewart, R.D. Sage, A.F. Stewart and D.W. Cameron, Breast cancer incidence
8 highest in the range of one species of house mouse, *Mus domesticus*, *Br J Cancer* 82
9 (2000) 446-51.
- 10 [385] A.F. Stewart, Identification of human homologues of the mouse mammary tumor virus
11 receptor, *Arch Virol* 147 (2002) 577-81.
- 12 [386] S. Indik, W.H. Gunzburg, P. Kulich, B. Salmons and F. Rouault, Rapid spread of mouse
13 mammary tumor virus in cultured human breast cells, *Retrovirology* 4 (2007) 73.
- 14 [387] J. Carpten, N. Nupponen, S. Isaacs, R. Sood, C. Robbins, J. Xu, M. Faruque, T. Moses,
15 C. Ewing, E. Gillanders, P. Hu, P. Bujnovszky, I. Makalowska, A. Baffoe-Bonnie, D.
16 Faith, J. Smith, D. Stephan, K. Wiley, M. Brownstein, D. Gildea, B. Kelly, R. Jenkins, G.
17 Hostetter, M. Matikainen, J. Schleutker, K. Klinger, T. Connors, Y. Xiang, Z. Wang, A.
18 De Marzo, N. Papadopoulos, O.P. Kallioniemi, R. Burk, D. Meyers, H. Gronberg, P.
19 Meltzer, R. Silverman, J. Bailey-Wilson, P. Walsh, W. Isaacs and J. Trent, Germline
20 mutations in the ribonuclease L gene in families showing linkage with HPC1, *Nat Genet*
21 30 (2002) 181-4.
- 22 [388] A. Zhou, B.A. Hassel and R.H. Silverman, Expression cloning of 2-5A-dependent
23 RNAase: a uniquely regulated mediator of interferon action, *Cell* 72 (1993) 753-65.
- 24 [389] A. Urisman, R.J. Molinaro, N. Fischer, S.J. Plummer, G. Casey, E.A. Klein, K. Malathi,
25 C. Magi-Galluzzi, R.R. Tubbs, D. Ganem, R.H. Silverman and J.L. DeRisi, Identification

- 1 of a novel Gammaretrovirus in prostate tumors of patients homozygous for R462Q
2 RNASEL variant, PLoS Pathog 2 (2006) e25.
- 3 [390] M. Ukita, H. Okamoto, T. Nishizawa, A. Tawara, M. Takahashi, H. Iizuka, Y. Miyakawa
4 and M. Mayumi, The entire nucleotide sequences of two distinct TT virus (TTV) isolates
5 (TJN01 and TJN02) remotely related to the original TTV isolates, Arch Virol 145 (2000)
6 1543-59.
- 7 [391] H. Okamoto, M. Takahashi, T. Nishizawa, M. Ukita, M. Fukuda, F. Tsuda, Y. Miyakawa
8 and M. Mayumi, Marked genomic heterogeneity and frequent mixed infection of TT virus
9 demonstrated by PCR with primers from coding and noncoding regions, Virology 259
10 (1999) 428-36.
- 11 [392] R.L. Hallett, J.P. Clewley, F. Bobet, P.J. McKiernan and C.G. Teo, Characterization of a
12 highly divergent TT virus genome, J Gen Virol 81 (2000) 2273-9.
- 13 [393] K. Takahashi, Y. Iwasa, M. Hijikata and S. Mishiro, Identification of a new human DNA
14 virus (TTV-like mini virus, TLMV) intermediately related to TT virus and chicken anemia
15 virus, Arch Virol 145 (2000) 979-93.
- 16 [394] P. Biagini, H. Attoui, P. Gallian, M. Touinssi, J.F. Cantaloube, P. de Micco and X. de
17 Lamballerie, Complete sequences of two highly divergent European isolates of TT virus,
18 Biochem Biophys Res Commun 271 (2000) 837-41.
- 19 [395] Y. Tanaka, D. Primi, R.Y. Wang, T. Umemura, A.E. Yeo, M. Mizokami, H.J. Alter and
20 J.W. Shih, Genomic and molecular evolutionary analysis of a newly identified infectious
21 agent (SEN virus) and its relationship to the TT virus family, J Infect Dis 183 (2001) 359-
22 67.
- 23 [396] F. Davidson, D. MacDonald, J.L. Mokili, L.E. Prescott, S. Graham and P. Simmonds,
24 Early acquisition of TT virus (TTV) in an area endemic for TTV infection, J Infect Dis 179
25 (1999) 1070-6.

- 1 [397] P. Gerner, R. Oettinger, W. Gerner, J. Falbrede and S. Wirth, Mother-to-infant
2 transmission of TT virus: prevalence, extent and mechanism of vertical transmission,
3 *Pediatr Infect Dis J* 19 (2000) 1074-7.
- 4 [398] J.K. Ball, R. Curran, S. Berridge, A.M. Grabowska, C.L. Jameson, B.J. Thomson, W.L.
5 Irving and P.M. Sharp, TT virus sequence heterogeneity in vivo: evidence for co-
6 infection with multiple genetic types, *J Gen Virol* 80 (Pt 7) (1999) 1759-68.
- 7 [399] C. Niel, F.L. Saback and E. Lampe, Coinfection with multiple TT virus strains belonging
8 to different genotypes is a common event in healthy Brazilian adults, *J Clin Microbiol* 38
9 (2000) 1926-30.
- 10 [400] H. Yotsuyanagi, Y. Shintani, K. Moriya, H. Fujie, T. Tsutsumi, T. Kato, K. Nishioka, T.
11 Takayama, M. Makuuchi, S. Iino, S. Kimura and K. Koike, Virologic analysis of non-B,
12 non-C hepatocellular carcinoma in Japan: frequent involvement of hepatitis B virus, *J*
13 *Infect Dis* 181 (2000) 1920-8.
- 14 [401] S.R. Kim, Y. Hayashi, M. Kudo, S. Imoto, K.B. Song, K. Ando, S. Shintani, T.
15 Koterazawa, K.I. Kim and M. Taniguchi, TTV positivity and transfusion history in non-B,
16 non-C hepatocellular carcinoma compared with HBV- and HCV-positive cases,
17 *Intervirology* 43 (2000) 13-5.
- 18 [402] P. Pineau, M. Meddeb, R. Raselli, L.X. Qin, B. Terris, Z.Y. Tang, P. Tiollais, V.
19 Mazzaferro and A. Dejean, Effect of TT virus infection on hepatocellular carcinoma
20 development: results of a Euro-Asian survey, *J Infect Dis* 181 (2000) 1138-42.
- 21 [403] E.M. de Villiers, R. Schmidt, H. Delius and H. zur Hausen, Heterogeneity of TT virus
22 related sequences isolated from human tumour biopsy specimens, *J Mol Med* 80 (2002)
23 44-50.
- 24 [404] P. Finzer, C. Kuntzen, U. Soto, H. zur Hausen and F. Rosl, Inhibitors of histone
25 deacetylase arrest cell cycle and induce apoptosis in cervical carcinoma cells

- 1 circumventing human papillomavirus oncogene expression, *Oncogene* 20 (2001) 4768-
2 76.
- 3 [405] L.H. Hartwell, P. Szankasi, C.J. Roberts, A.W. Murray and S.H. Friend, Integrating
4 genetic approaches into the discovery of anticancer drugs, *Science* 278 (1997) 1064-8.
- 5 [406] L.L. Villa, Prophylactic HPV vaccines: reducing the burden of HPV-related diseases,
6 *Vaccine* 24 Suppl 1 (2006) S23-8.
- 7 [407] I.H. Frazer, Prevention of cervical cancer through papillomavirus vaccination, *Nat Rev*
8 *Immunol* 4 (2004) 46-54.
- 9
10
11

1 **Figure Legends**

2

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]

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
-

1

2

ACCEPTED

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?)
-

1

2

ACCEPTED MANUSCRIPT

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

1

2

Table 4. Properties of viruses implicated in human cancers

Virus	Viral Taxonomy	Genome	Human Cancers
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?

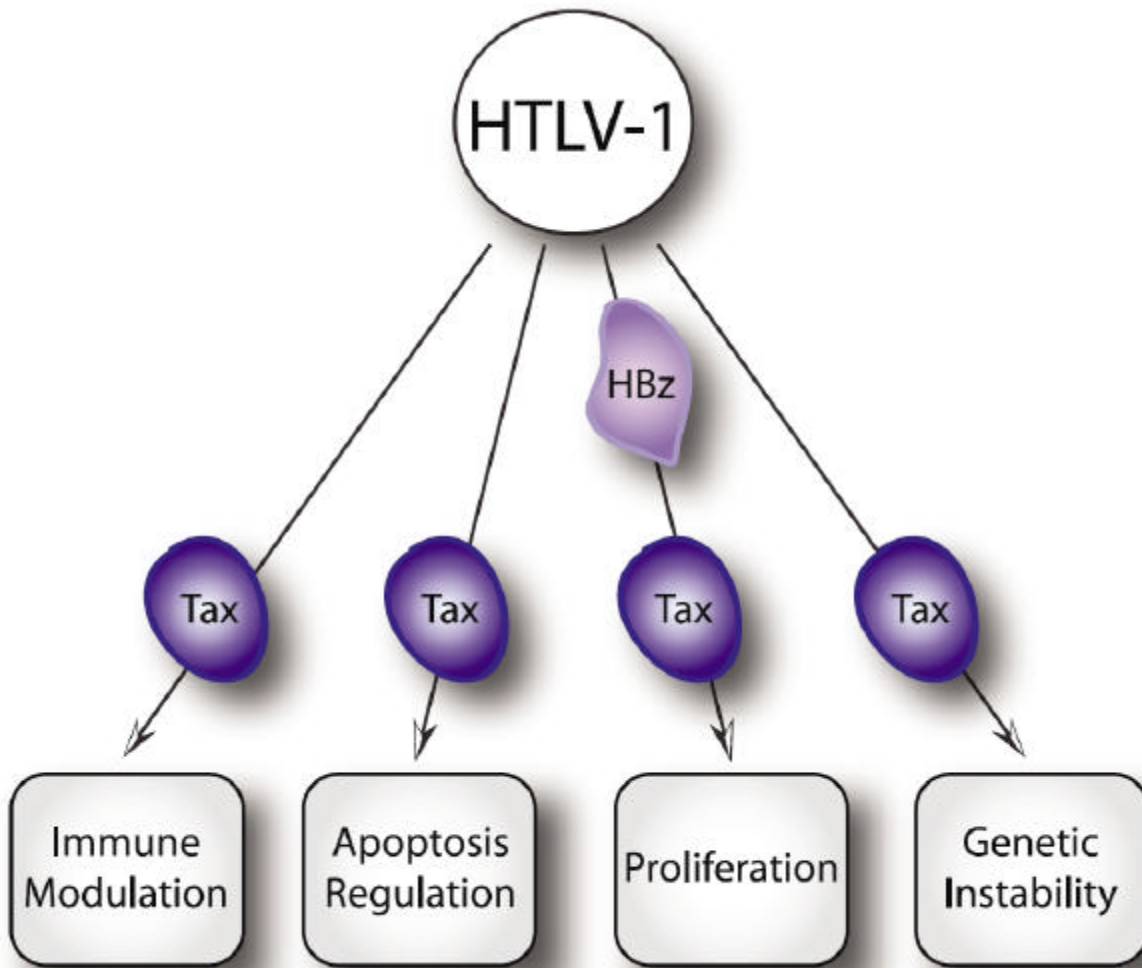
BKV, BK virus; HERVs, human endogenous retroviruses; HMTV, human mammary tumor virus; JCV, JC virus; SV40, simian virus 40; TTV, Torque Teno virus

1

2

ACCEPTED MANUSCRIPT

1

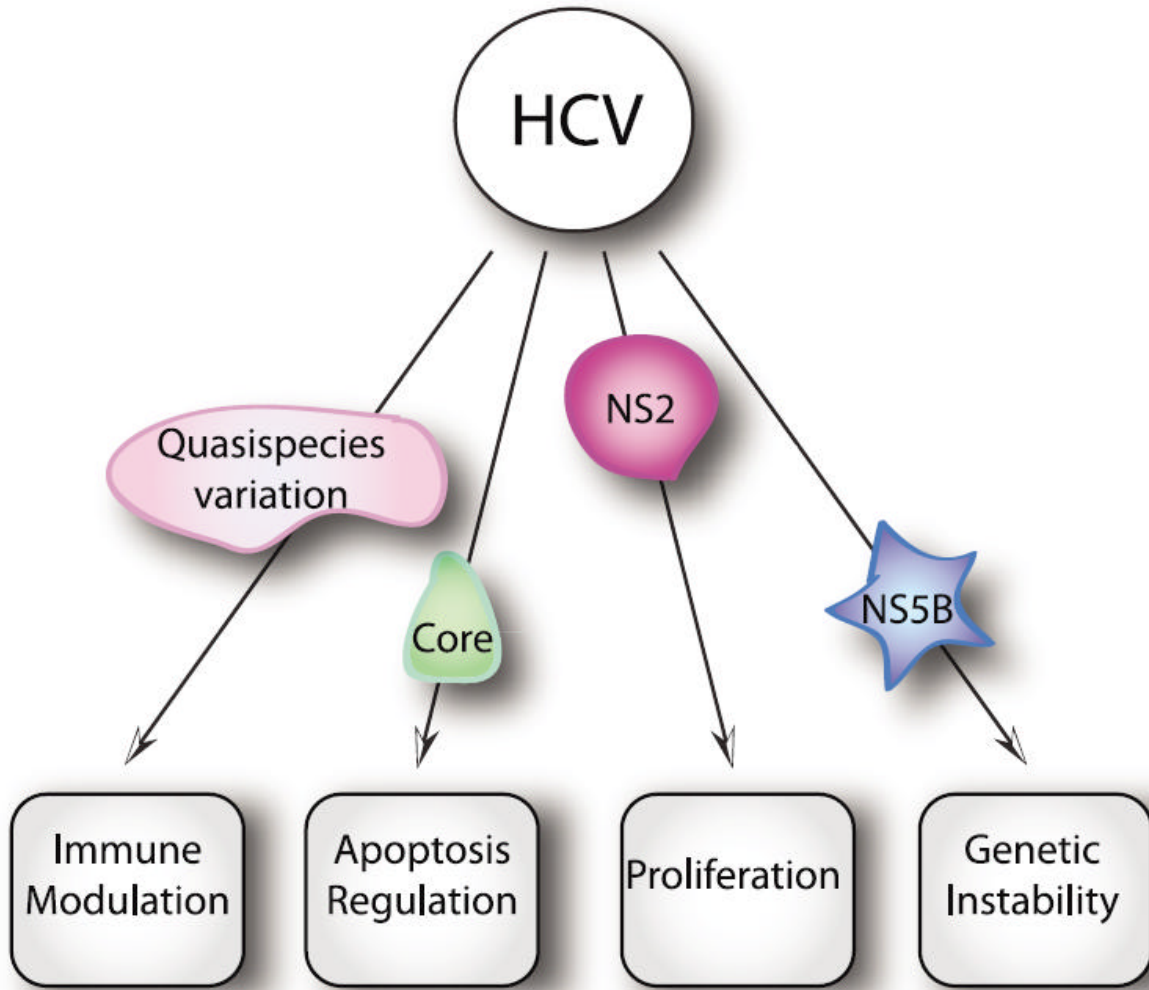


2

3

A

1

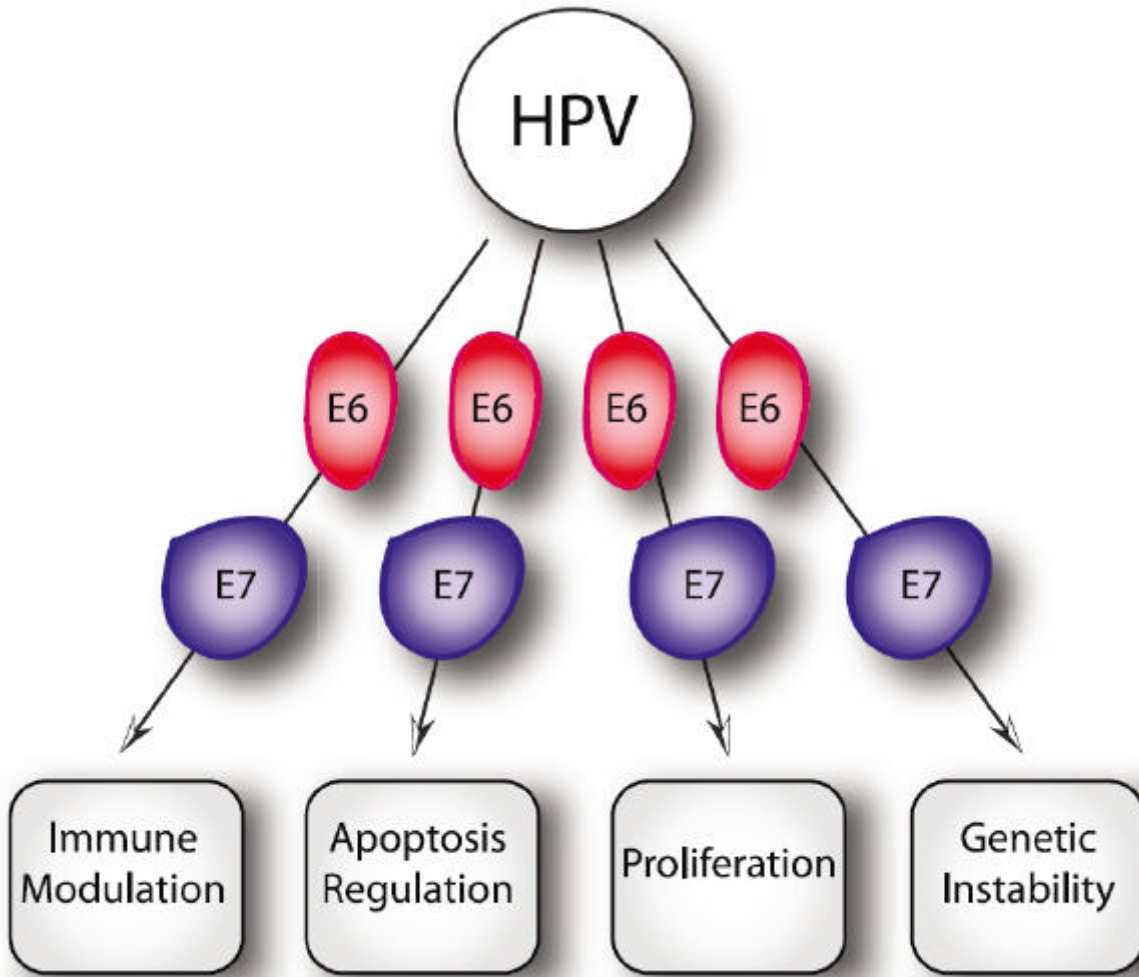


2

3

A

1

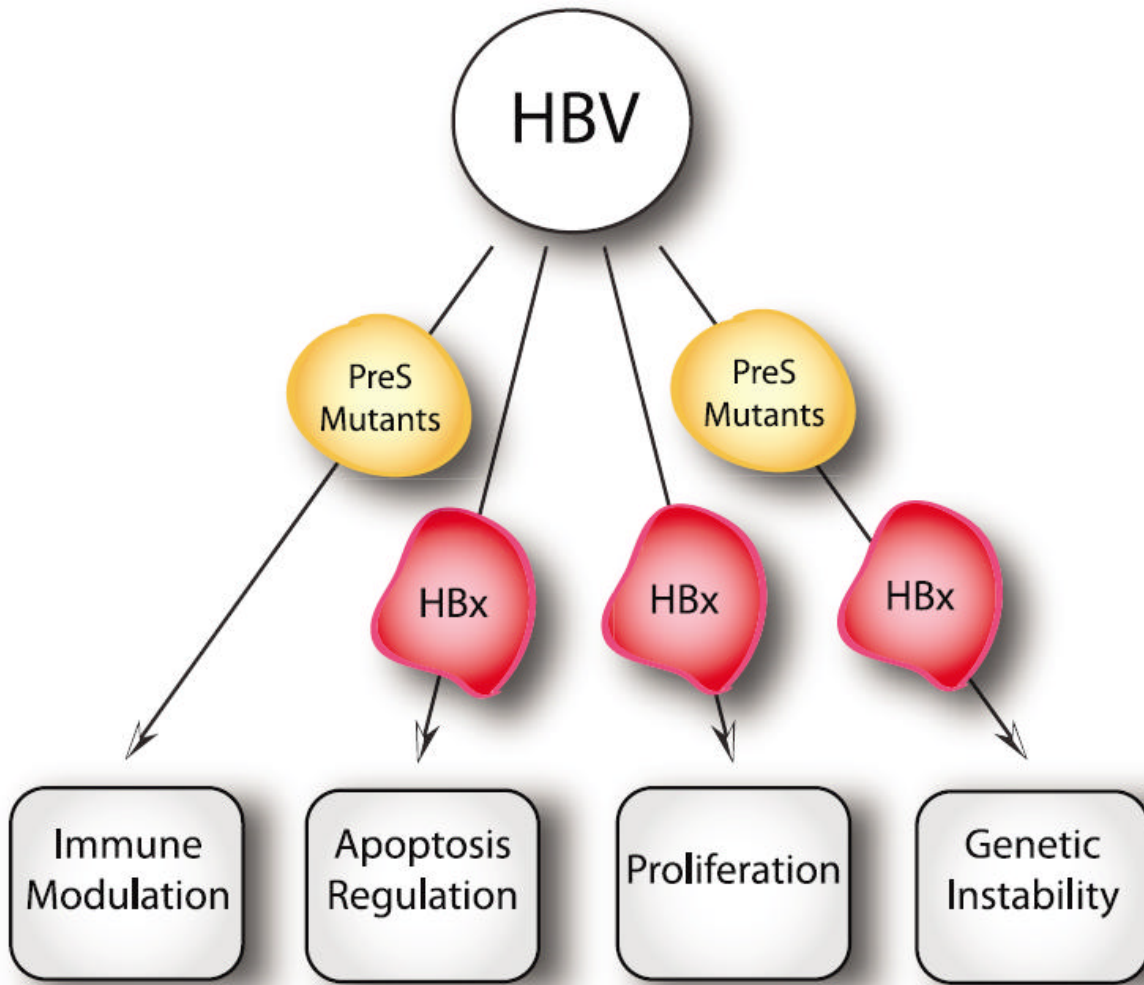


2

3

A

1

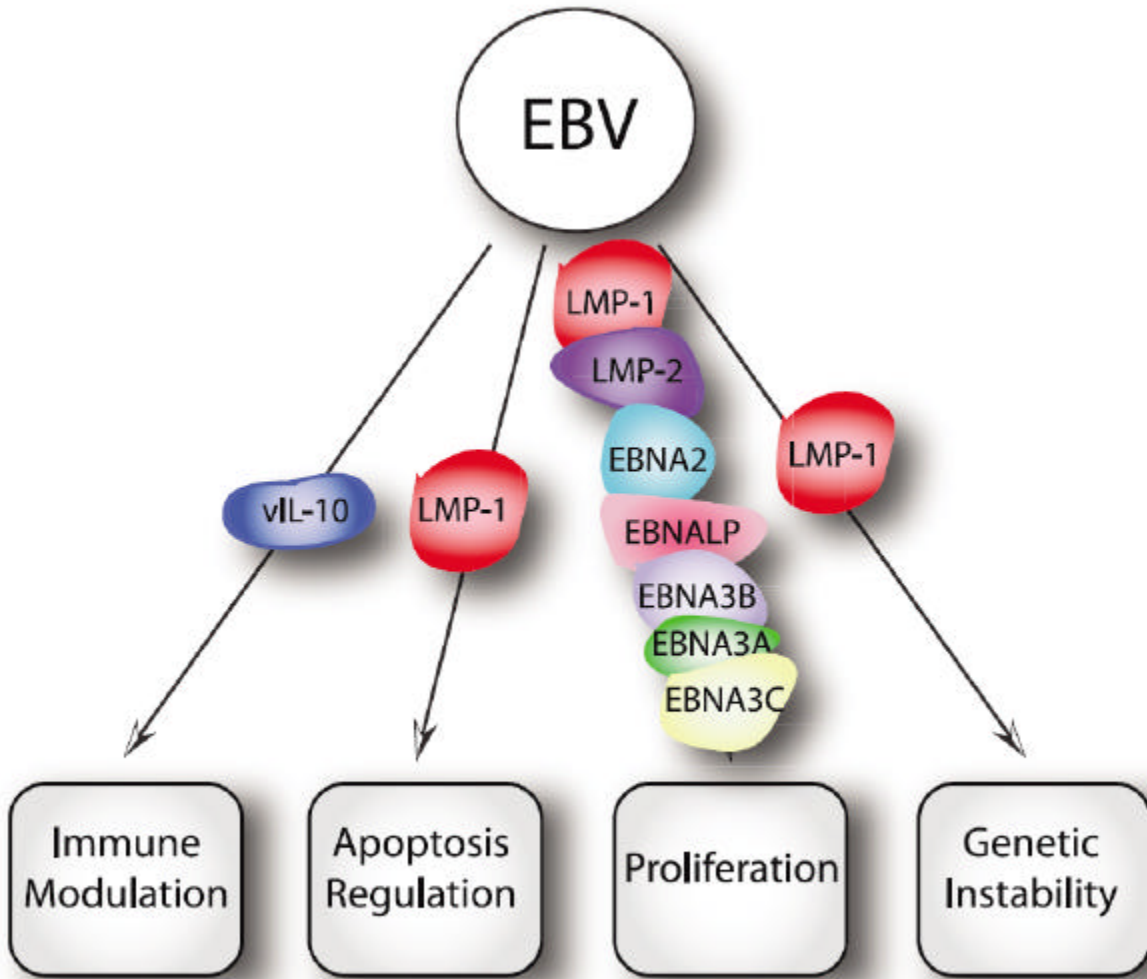


2

3

A

1

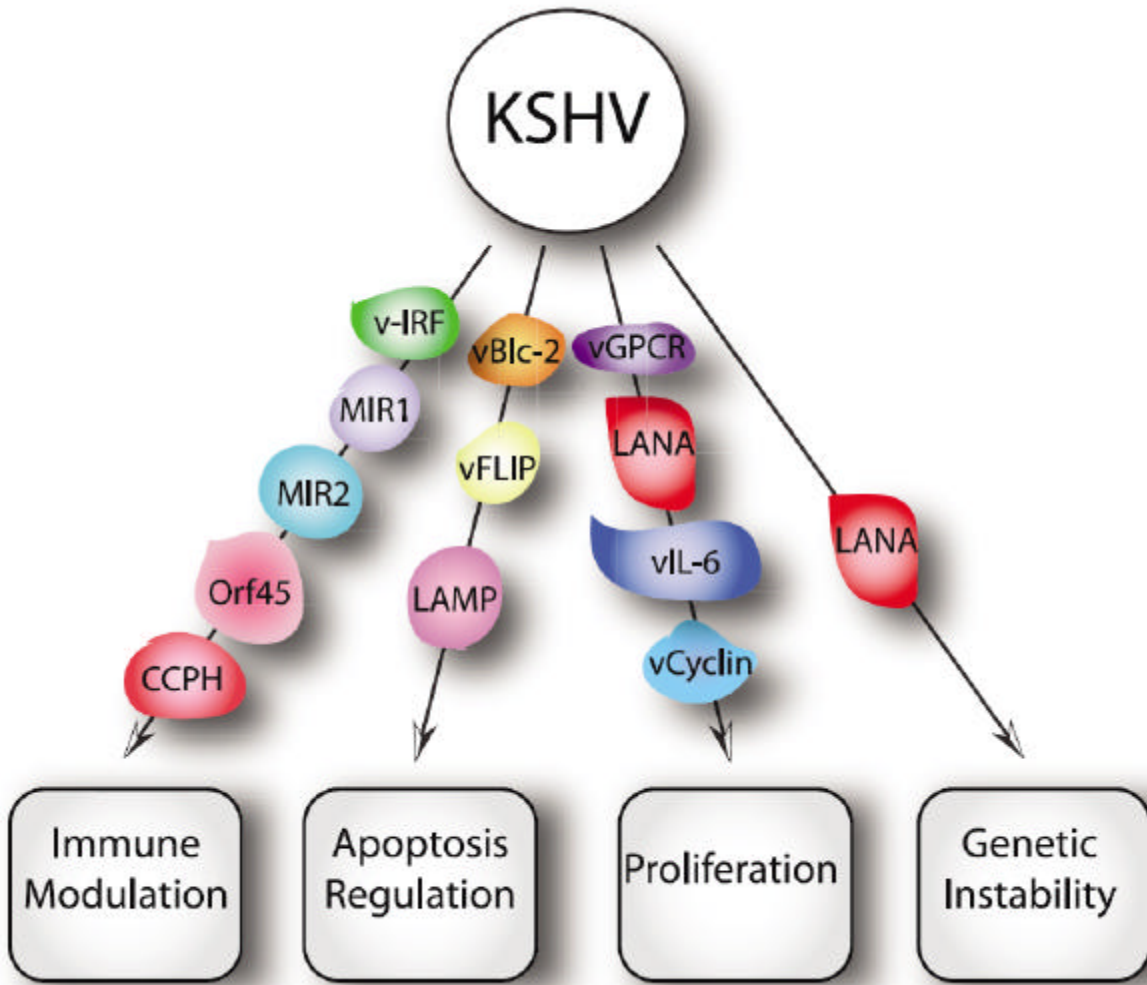


2

3

A

1



2

A