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REVIEW

Mechanisms of Viral Oncogenesis: DNA and RNA Viruses in Human Cancer

Nana Yao[1,2], Bo Huang[1]

[1]Department of Pathology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, 110000 People's Republic of China; [2]Department of Pathology, The 7th People's Hospital of Zhengzhou, Zhengzhou Cardiovascular Hospital, Henan, Zhengzhou, People's Republic of China

Correspondence: Bo Huang, Department of Pathology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, No. 44 Xiaoheyan Road, Dandong District, Shenyang 110000, People's Republic of China, Email huangbo@cancerhosp-ln-cmu.com

Abstract: With 13% of global tumorigenesis related to pathogens and 2.2 million new tumour cases related to viral infections every year, the role played by viruses in tumorigenesis cannot be ignored. At present, the viruses that have been identified as carcinogenic substances are EB virus, hepatitis B virus, hepatitis C virus, Kaposi's sarcoma virus, human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, human papillomavirus, Merkel cell polyomavirus, and BK virus. There are also a number of viruses which have not been designated as carcinogens, but which are also closely related to the tumours' development, such as Simian virus 40, JC virus and human cytomegalovirus. Human oncolytic viruses are divided into DNA oncolytic viruses and RNA oncolytic viruses, which are highly diverse and have different tumorigenic mechanisms. This article focuses on these confirmed DNA tumor viruses and RNA tumor viruses, delving into the various tumor types they cause and the mechanisms behind them. Based on the comparative analysis of their oncogenic pathways, we conclude that common mechanisms, such as the disruption of tumor suppressor proteins, chronic inflammation, and immune evasion, presenting actionable targets for both prophylactic intervention and precision therapy against virus-associated cancers.

Keywords: tumours, tumour virus, tumorigenic mechanism, SV40, mesothelioma

Introduction

The understanding of tumor pathogenesis is a long process, which has risen from the past single physical, chemical, biological and mutational carcinogenesis to a multi-step, multifactorial integrated carcinogenesis theory.[1] Tumors are not just a group of simple cancer cells, but a heterogeneous collection of invasive host cells, secreted factors and extracellular matrix, and the environment in which tumor cells live is decisive in tumor differentiation, epigenetics, metastasis and immune escape.[2] Another study proposed the concept of immune-tumor microbial axis also reveals the relationship between microbial communities and tumorigenesis and progression.[3] With the deepening research on the pathogenicity of viruses, scholars have increasingly discovered the significant role of viruses in tumor formation. The earliest discovery of the relationship between viruses and tumors can be traced back to 1911 when modern biology had not yet been established. It was during that time that the American pathologist Rous accidentally discovered a virus that could cause malignant tumors in chickens.[4] This seminal discovery undoubtedly marks a pivotal milestone in the field of oncogenic virology. The virus, ultimately named Rous Sarcoma Virus, was identified as a result of this groundbreaking observation. Dr. Rous's pioneering work in identifying the first oncogenic virus earned him the prestigious Nobel Prize in Physiology or Medicine. In subsequent research, John Bittner and Ludwik Gross respectively discovered the Mouse Mammary Tumor Virus, the Mouse Leukemia Virus, and the Polyomavirus in mice. John Bittner made his discovery in 1936, while Ludwik Gross made his discoveries in the early 1950s. With the deepening of research on the pathogenicity of viruses, scholars are increasingly discovering that viruses play an important role in the formation of tumors. The discovery of the relationship between viruses and tumors can be traced back to 1911. In an era before modern biology was established, American pathologist Rous accidentally discovered a virus that could cause malignant tumors in

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Table 1 Summary of DNA and RNA Tumor Viruses and Their Associated Tumors

Virus Type	Virus	Tumors
DNA Tumor Viruses	Polyomaviruses	Malignant mesothelioma, osteosarcoma, non-Hodgkin's lymphoma, brain tumors
	Human Papillomavirus (HPV)	Cervical cancer, vulvar cancer, vaginal cancer, anal cancer, oropharyngeal cancer, head and neck squamous cell carcinoma
	Epstein-Barr Virus (EBV)	Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, T/NK cell lymphoma, gastric cancer
	Kaposi's Sarcoma-Associated Herpesvirus (KSHV)	Kaposi's sarcoma, primary effusion lymphoma
	Human Cytomegalovirus (HCMV)	Glioblastoma, colon cancer, prostate cancer
	Hepatitis B Virus (HBV)	Hepatocellular carcinoma
RNA Tumor Viruses	Human T-cell Leukemia Virus Type 1	Adult T-cell leukemia/lymphoma
	Human Immunodeficiency Virus Type 1	Kaposi's sarcoma
	Hepatitis B Virus (HBV)	Hepatocellular carcinoma

poultry.[4] This discovery is undoubtedly a milestone in tumor virology research. The virus was eventually named Rous sarcoma virus, and Rous was awarded the Nobel Prize in Physiology or Medicine for being the first to discover tumor viruses; In subsequent studies, John Bittner and Ludwik Gross discovered mouse breast tumor virus, mouse leukemia virus, and mouse polyoma virus in 1936 and early 1950s, respectively;[5] In 1964, Michael Epstein and Yvonne Barr discovered the first human tumor virus, EB virus, in the lymphoblasts of Burkitt lymphoma patients.

At present, 13% of the world's tumors are associated with pathogenic agents, and 2.2 million new tumor cases each year are associated with viral infections,[6] based on the accumulation of a large number of experimental, clinical and epidemiological studies over the past 50 years. In 2020, the International Agency for Research on Cancer (IARC) identified Epstein Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma virus (KSHV), human immunodeficiency virus type 1 (HIV-1), Human T-cell lymphotropic virus type 1 (HTLV-1) and human papilloma virus (HPV) are classified as Group 1 human carcinogens. Two viruses, Merkel cell polyomavirus (MCPyV) and BK virus (BKV), are classified as Group 2 human carcinogens.[7,8] There are also a number of viruses that are not currently listed as carcinogens but have been shown to be associated with tumorigenesis, such as Simian virus 40 (SV40) of the polyomavirus family, JC virus (JCV), and human cytomegalovirus (HCMC) of the herpesvirus family. The common feature of these human tumor viruses is that through long-term and continuous infection of host cells, they induce cell proliferation and division to produce genetic mutations, which ultimately lead to tumorigenesis, rather than directly killing the host cells; on the other hand, after the viruses enter the host cells, their genes are integrated into the host cells and thus regulate the physiological functions of the host to promote tumorigenesis.

Human oncolytic viruses are highly diverse and can be classified into DNA oncolytic viruses and RNA oncolytic viruses, which have different tumorigenic mechanisms. Knowing the relationship between these DNA and RNA oncolytic viruses and the occurrence of human neoplastic diseases and understanding the tumorigenic mechanism of human oncolytic viruses will help us to better understand the development of tumors and contribute to the prevention of virus-associated neoplastic diseases. While preventive interventions like vaccination and antiviral therapies have successfully reduced the incidence of certain virus-related cancers, the molecular intricacies of how viral proteins modulate host cell signaling networks remain a subject of intense research. Recent reviews have provided broad overviews of the field or focused on therapeutic strategies.[9–11] However, a comparative and quantitative synthesis of the latest mechanistic findings is lacking. In this paper, we summarize the oncogenicity of DNA and RNA oncolytic viruses and their oncogenic mechanisms as follows. The specific tumors caused by DNA and RNA viruses are summarized in Table 1.

DNA Tumour Virus

DNA viruses are biological viruses whose nucleic acid is DNA and are mainly transmitted through blood, saliva, respiratory tract, sexual contact, fecal-oral and mother-to-child routes, and their sources of infection mainly include patients and asymptomatic carriers of the virus. DNA viruses are classified into double-stranded DNA viruses and single-stranded DNA viruses according to the type of viral nucleic acid and how the mRNA is transcribed, and among them, DNA oncolytic viruses' nucleic acids are double-stranded. The double-stranded DNA structure of DNA tumor viruses allows their genetic material to integrate directly into the DNA of the host cell, affecting the host cell cycle and influencing tumor growth by encoding a number of antigens and oncoproteins. The human tumor-associated, common DNA tumor viruses are polyomaviruses, papillomaviruses, herpesviruses, and hepatophilic DNA viruses. The basic structure of these viruses consists of nucleic acids and capsids, some of these DNA oncolytic viruses have an envelope structure eg HPV, EBV, KSHV and HCMV, while others are naked icosahedral viral particles eg HPV, polyomaviruses.

Polyomaviruses

Polyomaviruses all have a small, circular, double-stranded DNA genome encased in icosahedral viral particles. SV40 is a monkey vacuolar virus40 that accidentally infected humans through contaminated polio vaccine between 1955 and 1963.It belongs to the family Polyomaviridae. It is now believed that SV40 may be excreted in the urine of infected hosts and can also be transmitted through the digestive and respiratory tracts. Subsequently, in 1971, the first two human polyomavirus isolates, BKV and JCV, were identified. In addition, Merkel cell polyomavirus is currently the only member of the polyomavirus family that has been scientifically proven to have the ability to cause oncogenic changes in humans.[12] Three regions have been identified in the genome of polyomaviruses: the non-coding region, the early coding region, and the late coding region. The non-coding region includes the replication start promoter, whose nucleotide sequence is the binding site for transcription factors that regulate the early and late gene schedules. The terms "early" and "late" indicate the temporal order of gene transcription during the viral life cycle in the host cell and are transcribed in opposite directions. The early region encodes the large T antigen (Tag) and the small t antigen (tag); the late region encodes the viral capsid proteins VP1, VP2, VP3, and VP4,[13] which form the outer shell of the viral particles and play an important role in the binding of viruses to cell surface receptors.

Tumorigenic Mechanism of Polyomavirus Infection

The large T antigen is a multifunctional phosphoprotein that is used to initiate the replication of viral DNA and to promote host cell entry into S phase and then DNA synthesis.[14] The tag is a non-phosphorylatable protein but functions like the large T antigen. In addition, both proteins have transforming potential in vitro and oncogenic activity in vivo. When cells are infected with polyomaviruses, these antigens bind and block important tumor suppressor proteins such as p53, pRb, p107, and p130/Rb2. Tag binds to p53 and inhibits its function and allows genetically damaged cells to survive and enter S phase, where the Tag-p53 complex binds and activates insulin-like growth factors-1 (IGF-1). The Tag-p53 complex binds to and activates IGF-1, which accelerates tumor cell growth. The tag can interact with protein phosphatase 2A (PP2A) to affect cell transformation. tag-PP2A complex induces cell entry into S-phase through degradation by the CDK inhibitor p27 and promotion by cyclinA/CDK2 and cyclinE/CDK2.[15,16] It has also been reported that JCV encodes T' proteins by splicing at an early stage, which are identical to the amino acid sequence of the large T antigen, and that they can play a role in cellular transformation by interacting with the tumor suppressor proteins p107 and p130.[17,18] The pathogenesis mechanism of polyomavirus is shown in Figure 1.

Neoplastic Diseases Associated with Polyomavirus Infection

Whether SV40 is associated with tumorigenesis is still controversial, but early studies have demonstrated that SV40 is able to replicate in human cells and that different human cell types exhibit differences in susceptibility to infection with SV40,[19] and that human mesothelial cells are transformed to SV40 at a rate at least 1,000-fold higher than that of human fibroblasts.[20] In 1994, Carbone et al[21] first identified the presence of SV40 DNA sequences in human malignant pleural mesothelioma tissues and subsequently found that 83% of mesotheliomas carried the SV40 gene by PCR. An analysis of reports of SV40 associated with human cancer was performed by Butel Laboratories,[22] which used strict inclusion criteria as well as the same laboratory techniques for both case and control groups, on 15 studies from The analysis of 996 subjects (528 mesothelioma patients and 468 controls) revealed a strikingly high odds ratio (OR = 15.1) for the association between SV40 and malignant pleural mesothelioma, indicating a profound increase in risk. Furthermore,

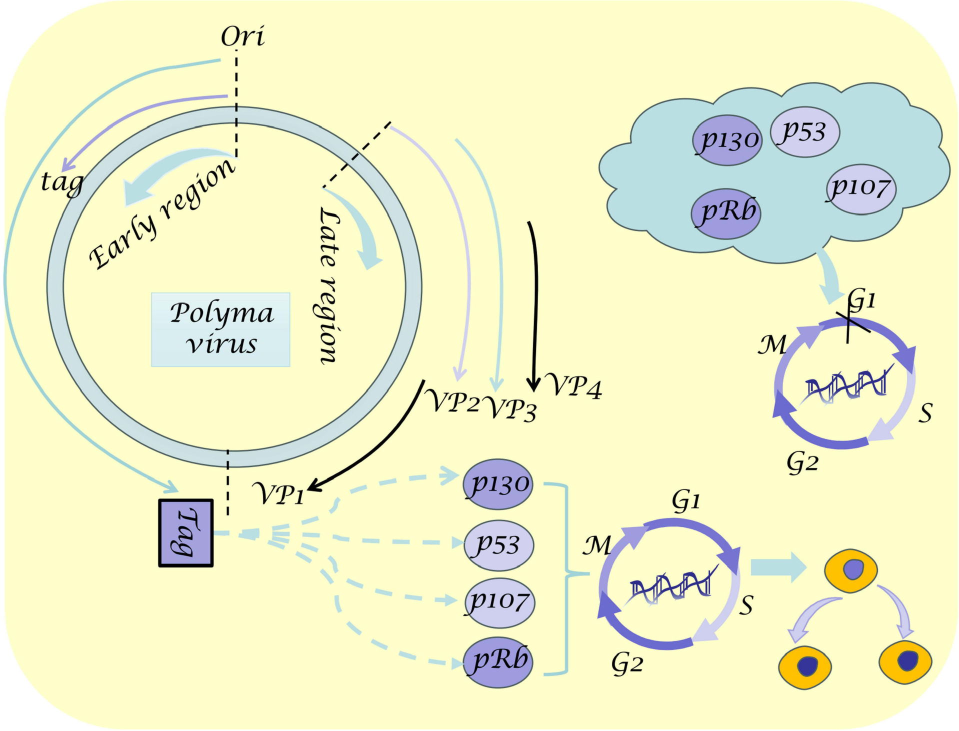

Figure 1 Pathogenesis Mechanism of Polyomavirus.

significant associations were also observed for brain tumors (OR = 3.8), osteosarcomas (OR = 24.5), and non-Hodgkin lymphomas (OR = 5.4). Mazzoni et al[23] tested serum IgG antibodies to SV40 Tag by indirect ELISA on serum samples from 249 osteosarcoma patients and 247 normal subjects, and the results showed that there was an association between osteosarcoma patients and SV40 Tag, and that SV40 may be a cofactor in the development of osteosarcoma.

Merkel cell carcinoma is caused by Merkel polyomavirus, which is a rare and aggressive human cutaneous neuroendocrine tumor with a high mortality rate. It has also been shown that MCPyV DNA has been detected in squamous carcinoma of tonsils, thymoma, esophageal carcinoma, hepatocellular carcinoma, and salivary gland carcinoma using qPCR,[24–26] and although it is not yet possible to prove the potential role of MCPyV with in these tumors, these findings provide some ideas for the study of this virus. JCV DNA was detected in a high proportion (69%, 49/71) of brain tumor samples,[27] and BKV DNA was identified in an overwhelming majority (94%, 17/18) of neuroblastoma cases.[28]

Human Papillomavirus (HPV)

HPV is a double-stranded circular DNA virus with a lipoprotein-free membrane, core and capsid proteins, and is one of the most common viruses responsible for infections of the reproductive system. More than 200 HPV types have been identified. According to the relationship with cervical cancer, HPV can be categorized into high-risk HPV (hrHPV) and low-risk HPV (lrHPV).The HPV genome can be divided into three coding regions: the early region, the late region, and the upstream regulatoryregion (URR), the E region encodes the oncoprotein E1-7 associated with viral replication, and the L region encodes two late coat proteins, L1 and L2.HPV DNA can exist in two forms in the organism, ie, the free form and the integrated form, and HPV DNA exists mostly in the free form in benign lesions and in the integrated form in malignant tumors.

Tumorigenic Mechanism of HPV Infection

hrHPV mainly binds to the body oncoprotein p53 by encoding oncoprotein E6, which causes p53 to lose its normal function, leading to the initiation of DNA repair, apoptosis, or growth arrest of host cells, and angiogenesis is also

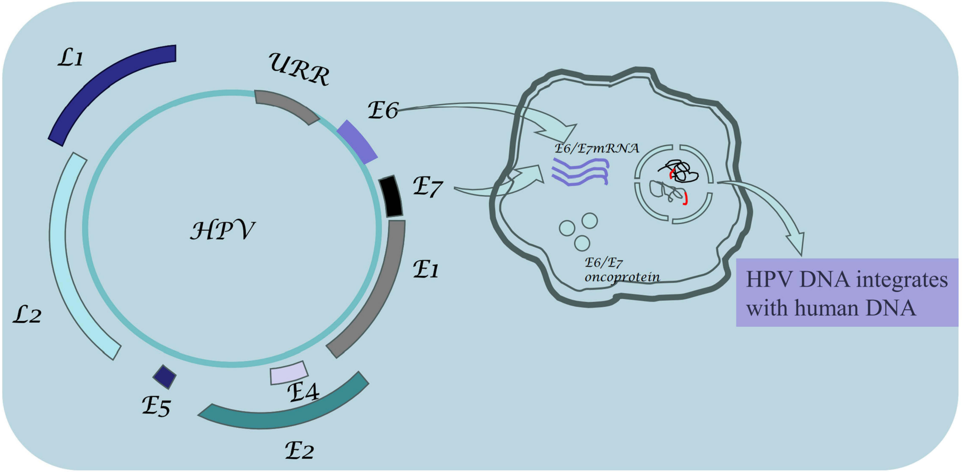

Figure 2 Structure and Pathogenic Mechanism of HPV.

disrupted. At the same time, oncoprotein E7 binds to retinoblastoma binding protein (pRb), thereby releasing the transcription factor E2F, causing the cells to re-enter S phase, which in turn leads to tumorigenesis.[29] And there have been studies in animal models that have found that anti-HPV16 E6 and E7 protein antibodies can cause tumor cell apoptosis to delay tumor progression, which suggests a new treatment for HPV-associated lesions.[30] Furthermore, a study diagnosed 210 patients with Cervical Intraepithelial Neoplasia grade II (CINII) through colposcopy-guided biopsy from April 2017 to April 2019. These patients were also tested positive for HPV E6/E7 mRNA. They underwent colposcopy examination, HPV testing, E6/E7 mRNA testing, and p16 protein testing every 6 months. It was found that as the CIN level increased in hrHPV-infected individuals, the positivity rate and relative expression of HPV E6/E7 mRNA also increased, showing a positive correlation with CIN grading.[31] Furthermore, the majority of epidemiological and in vitro studies have suggested[32,33] that methylation of the L1, L2, E5, and E2 regions of different hrHPV genotypes can collectively contribute to the progression of cervical cancer. Oxidative damage and inflammatory responses have also been identified as synergistic factors in tumor progression. The pathogenic mechanism of HPV is shown in Figure 2.

Neoplastic Diseases Associated with HPV Infection

HPV has the characteristic of complex squamous epithelium, and thus can easily cause infections in tissues or organs with complex squamous epithelium, such as the cervix, vulva, vagina, mouth, and pharynx. lrHPV mainly leads to wart-like lesions, while hrHPV can cause cervical cancer and CIN. Current studies have further shown that HPV is not only closely related to cervical cancer, but also can cause vulvar, penile, vaginal, anal, oropharyngeal, and head and neck squamous cell carcinomas.[34–37] Recently Silvia et al[38] collected a total of 18,247 paraffin-fixed specimens from 50 countries for HPV DNA testing by PCR, and showed that 22.4% of oropharyngeal cancers, 4.4% of oral cancers, and 3.5% of laryngeal cancers were caused by HPV. Moreover, it was found that the nine-valent HPV vaccine could prevent the HPV-positive anal cancers (96%), vulvar cancers (93%), cervical cancer (90%), penile cancer (88%), vaginal cancer (86%), oropharyngeal cancer (95%), oral cancer (93%) and laryngeal cancer (78%).

Herpesvirus

Epstein-Barr Virus (EBV)

EBV is a human lymph cytophilic double-stranded DNA virus that infects humans and belongs to the human herpesvirus subfamily γ. It infects 90% of the global population and was the first virus found to be associated with human neoplasia, mainly through close contact in the oral mucosa, while other modes of transmission include blood and sexual transmission. It is associated with a wide range of human diseases, including non-neoplastic diseases: infectious mononucleosis, chronic active EBV infection, virus-associated hemophagocytic syndrome and neoplastic diseases. It is estimated that there are about 200,000 new cases of EBV-associated tumors each year, and deaths account for about 1.8% of all malignant tumor deaths each year.[38]

Tumorigenic Mechanism of EBV Infection

Cellular invasion is the first step in EBV's infection of host cells to cause disease. Like otherγherpesviruses, EBV establishes latent infection in lymphocytes and induces proliferation of latently infected cells to cause disease. B cells and epithelial cells are the main host cells for EBV, with NK/T lymphocytes being less frequently infected. EBV infection of B cells first occurs through the viral envelope glycoprotein gp350/ 220 binds with high affinity to B cell-specific complement receptor 2 (CR2 or CD21) and adheres to the B cell surface and undergoes endocytosis. At this point EBV gp42 binds to B cell HLA class II molecules mediating fusion enabling the release of viral particles into the B cell, which instead undergoes self-replication to facilitate viral invasion.[39] This interaction can block the recognition of T lymphocytes, thereby evading immune system surveillance. Additionally, EBV can encode proteins to interfere with MHC class I molecules, thereby limiting the antigen recognition of $CD8^+$ cytotoxic T cells for immune evasion. Although epithelial cells lack CR2 receptors and the expression of human HLA class II antigens, EBV particles released from B lymphocytes lack the expression of gp42 and can no longer infect B cells, which allows them to effectively infect epithelial cells. The role of epithelial cells may be as a site for EBV replication and amplification rather than a site for persistent latent infection. Shortly after EBV infection, a program including all latent proteins, six EBV nuclear antigens (EBNAs), and three membrane proteins (LMP1, LMP2A, LMP2B) is activated. The latent membrane protein LMP1, expressed in most EBV-associated lymphoproliferative lesions and malignancies, is the principal oncogenic protein of the virus and plays a key role in tumor promotion. Furthermore, LMPs mediate cellular transformation and immortalization, inhibit apoptosis, and promote cell motility, invasion, and metastasis, which are crucial to the pathogenesis following EBV infection. EBV infection primarily expresses six types of nuclear antigens including EBNAs (EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNALP),[40] among which EBNA1 is the only protein expressed in all types of EBV-associated malignancies, aiding in the maintenance, replication, and transformation of viral episomes[41] Although all diseases associated with EBV involve a latent phase of the virus, during the lytic phase, malignant tumors can also be caused and maintained through the induction of growth factors and oncogenic factors, as well as enhanced expression of cytokines and growth factors to maintain EBV's latent infection and promote the transformation and proliferation of cells harboring latent EBV.[42] The pathogenic mechanism of EBV is shown in Figure 3

Neoplastic Diseases Associated with EBV Infection

EBV is associated with a wide range of neoplastic diseases and the distribution of its associated malignancies has significant geographic variation, which may be related to host genetic background, environmental climate, and dietary habits, and it has also been suggested that this may be related to the mutation of EBV strains.[43] EBV was initially found in lymphoblastoid cells from patients with Burkitt lymphoma, which has three subtypes, in which EBV is detected in tumor tissue in almost 100% of endemic Burkitt lymphoma cases,[44] and epidemiological and serological studies have shown a causal relationship between EBV infection and Burkitt lymphoma. In addition, EBV has been associated with Hodgkin's lymphoma and EBV genome positivity varies among the different pathologic subtypes of this disease, especially the mixed-cell subtype, which is most closely associated with EBV. Nasopharyngeal carcinoma, an epithelial cancer associated with EBV, is commonly found in southern China and Southeast Asia, and more than 97% of nasopharyngeal carcinomas are EBV-positive.[45] T/NK-cell lymphomas belong to a rare and specific type of extra-lymph node non-Hodgkin's lymphoma, which accounts for 5%–15% of non-Hodgkin's lymphomas, and is seen predominantly in Asia and Native Americans, and is almost always associated with EBV infection. EBV DNA can be detected in the lesions of patients with T/NK-cell lymphoma, and viral loads can decrease with treatment. Another malignancy associated with EBV infection is gastric cancer. EBV-associated gastric cancer (EBVaGC) accounts for approximately 8.7% of all gastric cancers and is a subtype of gastric cancer with distinctive clinicopathological features, predominantly occurring in males, with no geographic distributional differences.[46,47] There are also lymphoepithelial carcinomas occurring in the salivary glands, lung, cervix, and thymus that are frequently associated with EBV infection, but there is no evidence that EBV plays a specific role in these tumors.[48] He et al[49] performed EBER in situ hybridization

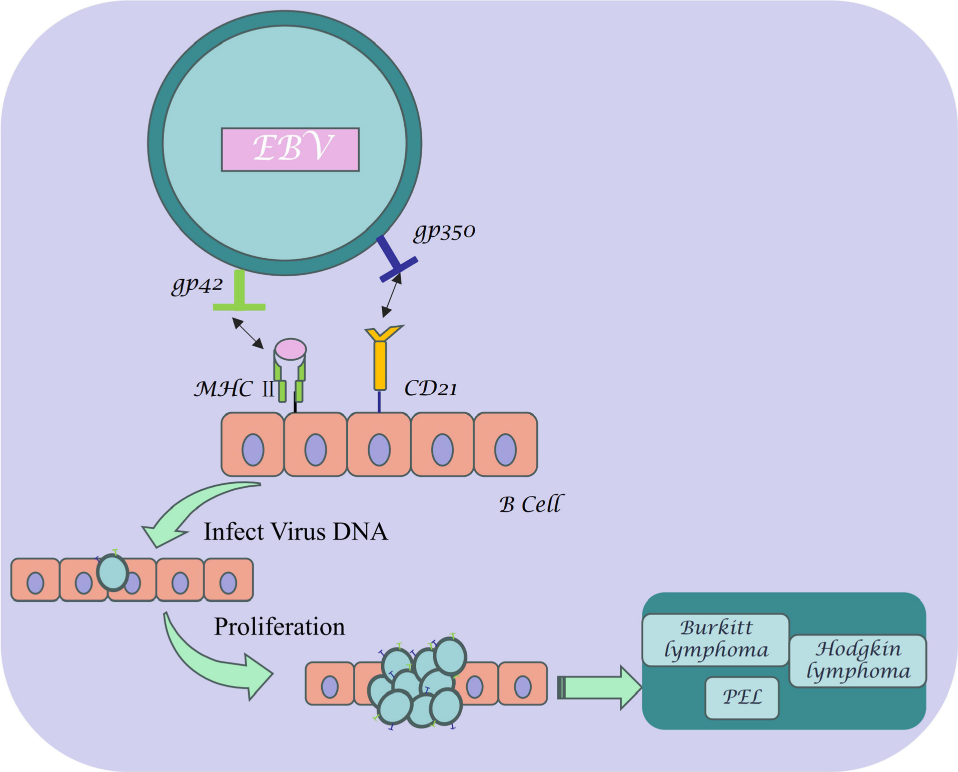

Figure 3 Pathogenic Mechanism of EBV.

on paraffin samples from 39 primary lymphoepithelioma-like carcinomas, of which 36 were positive. Primary effusion lymphoma (PEL) is a clonal, B-cell-originated tumor that occurs in fluid body cavities, and PEL is often co-infected with EBV in addition to KSHV infection.[50]

Kaposi's Sarcoma Virus (KSHV)

Kaposi's sarcoma virus (KSHV) is the eighth human herpesvirus discovered, also known as human herpes virus 8 (HHV-8), which is an enveloped, double-stranded DNA virus with a genome of approximately 170 kb. Both KSHV and EBV belong to the subfamily of human herpesviruses, subfamily γ, and are human oncolytic viruses, but, unlike most other herpesviruses, KSHV infection is not widespread.[51] It is primarily spread among populations through saliva,[52] but can also be transmitted through sexual contact, especially among males engaging in sexual relations.

Tumorigenic Mechanisms in KSHV Infection

Currently, the oncogenic mechanism of KSHV is not well understood. Its pathogenic infection is closely related to the host's immune response. When the host's immune system is strong, the number of KSHV-infected cells is low. Conversely, when the host's immune system is weak (such as in patients with AIDS), the detected viral copy numbers are high.[53,54] Among oncogenic viruses, KSHV has the most potential oncogenes.[55] It can enter dendritic cells, macrophages, and B cells, replicate within cells, and influence their functions, thereby promoting the transformation of host cells into tumors.[56] KSHV infects cells in two phases, latency and lysis, and it can encode a variety of specific proteins involved in cell cycle regulation, apoptosis and cytokine regulation.[57] The genes expressed during latency are crucial for KSHV-related tumorigenesis. During latency, KSHV can express LANA, vCyclin, vFlip, Kaposin B, and a cluster of miRNAs.[58] LANA is a nuclear protein functionally similar to EBV EBNA-1, which attaches KSHV segments to host chromosomes by associating with cellular chromosome-associated proteins thereby making the persistence of the KSHV staining fragment, which also interferes with various cellular pathways including the tumor suppressors p53 and pRb. vCyclin, a virally encoded homologue of the human cyclin D2, is involved in p53-dependent cell cycle arrest and induction of apoptosis. vFlip, the viral FLICE inhibitory protein, interferes with apoptosis mediated by the death receptor, causing persistent infection and tumor production.[59] Kaposin B mainly cooperates with latent gene transcripts to induce sarcoma formation. miRNAs encoded by KSHV can promote tumorigenesis by participating in immune regulation, apoptosis and angiogenesis. Whereas the transition from the latent phase to the lysogenic phase is the beginning of KSHV pathogenicity, genome replication in the lysogenic phase is important for viral invasion and spread.[60] The latent phase expresses cytokines and chemokines vIL-6, vCCL1, vCCL2, and vCCL3. vIL-6 induces dysregulation of IL-6 expression in immune cells and induces proliferation of myeloma cells in in vitro cultures, as well as inhibits host apoptotic histone protease D, which contributes to the maintenance of tumor cell activity. The chemokines vCCL1, vCCL2, and vCCL3 can interfere with effective communication between innate and adaptive immune cells allowing immune escape of KSHV-infected cells.[61,62]

Neoplastic Diseases Associated with KSHV Infection

KSHV is the causative agent of Kaposi's sarcoma and has also been associated with a variety of lymphoproliferative disorders, including PEL, extracorporeal primary exudative lymphoma, KSHV-associated multicentric Castleman's disease, and KSHV+ diffuse large B lymphoma.[50,63] KSHV has also been implicated in the development of tumors in other systems, and Su et al[64] examined KSHV antibodies and DNA in blood samples from 109 lung cancer patients and 109 healthy controls for antibodies and DNA to KSHV in their blood samples, and found that the serologic positivity rate of KSHV in lung cancer patients (50.8%) was almost one-fold higher than that of controls (24.8%), which suggests that KSHV may be associated with the development of some lung cancers. Paradzik et al[65] reported that more than half of the biopsy specimens of 55 patients with bladder cancers of varying degrees of malignancy were positive for KSHV DNA, and It is believed that it may be involved in bladder carcinogenesis, and the serologic positivity rate of KSHV has been documented to be as high as 39.9% in men with prostate cancer in the Tobago region of Japan.[66]

Human Cytomegalovirus (HCMV)

HCMV is a widely prevalent DNA virus, with a seroprevalence of over 50% in adult serum and reaching up to 70%–100% in developing countries.[67,68] Like most herpesviruses, HCMV typically remains in a latent infection without clinical manifestations in healthy individuals. However, when the host's immune system is compromised or immunosuppressed, it can facilitate the transformation of host cells into malignancies, closely associated with the development of malignant tumors.

Tumorigenic Mechanisms of HCMV Infection

Currently, the oncogenic mechanism of HCMV infection is unclear. Wang et al infected human glioblastoma cell line U87 with HCMV AD169 strain and detected the expression of STAT3 in HCMV-infected U87 cells using Western blotting. They also measured the mRNA expression levels of endothelial cell-specific molecule 1 (endocan) in HCMV-infected U87 cells using real-time quantitative PCR. STAT3, an important regulator of embryonic development and differentiation, especially in the development of neural stem cells and astrocytes, is abnormally overexpressed in tumor tissues and cells, contributing to the invasion and metastasis of tumor cells. Endocan is involved in processes such as cell adhesion, inflammation, and tumor formation. The study suggests that HCMV may upregulate endocan via the JAK2/STAT3 pathway to participate in the development of malignant tumors. In glioblastoma, HCMV alters cellular signaling by expressing viral G protein-coupled receptors (GPCRs). These viral receptors, homologous to human chemokine receptors, are encoded by four GPCRs in the HCMV genome, with one receptor, US28, expressed in glioblastoma cells, regulating tumor characteristics. UL33, another GPCR encoded by HCMV, has been shown to activate multiple proliferation, angiogenesis, and inflammation signaling pathways in glioblastoma cell lines, making it a potential target for treating HCMV-related malignant tumors.[69] In colorectal cancer, HCMV infection may promote tumor cell proliferation, inhibit apoptosis, and enhance the proliferation and invasion capabilities of colorectal cancer cells by regulating the expression of genes such as C-myc, Bcl-2, and p53.[70–72]

Neoplastic Diseases Associated with HCMV Infection

One study detected HCMV IgG in 12 glioma serum samples by peptide microarray.[73] Ninib et al[74] conducted PCR testing on paraffin samples from 37 cases of pediatric cerebral neuroblastoma, detecting HCMV DNA in 8 cases. Reverse experiments with immunodeficient mice led to the conclusion that HCMV could be a novel therapeutic target for this tumor. Additionally, another study[75] found that the expression positivity and immunohistochemical scores of HCMV viral proteins IE1-72 and pp65 in colon cancer patient tissues were higher than those in adjacent tissues, suggesting that HCMV infection may be involved in the occurrence of colon cancer. In another study by Oscar et al,[76] PCR testing for Helicobacter pylori and HCMV DNA was conducted on 106 cases of chronic gastritis patients and 32 cases of gastric cancer patients. HCMV and Helicobacter pylori infections accounted for 52.8% and 53.1% in chronic gastritis and gastric cancer, respectively. The study found a synergistic effect of HCMV and Helicobacter pylori on the occurrence of gastric cancer. Minu et al[77] randomly selected paraffin-embedded specimens from 22 cases of prostatic intraepithelial neoplasia and prostate cancer patients, using immunohistochemistry, in situ hybridization, PCR, and DNA sequencing methods, and discovered that persistent HCMV infection in prostatic epithelium may lead to prostatic intraepithelial neoplasia and prostate cancer.

Hepatophilic DNA Virus

HBV is a hepatophilic DNA virus, consisting of an envelope and capsid, and its DNA molecule consists of only 3200 nucleotides encoding hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and DNA polymerase, of which HBsAg is of great significance in diagnosing HBV infection. At least nine genotypes of HBV (types A through I) and one undetermined genotype (type J) have been identified, with genotypes B and C predominating in China. HBV genotypes have been associated with clinical outcomes, with genotype C being more strongly associated with severe liver disease, cirrhosis, and hepatocellular carcinoma (HCC) than the other genotypes (HR = 2.83) in a study conducted in Asia.[78] China is a highly endemic area for HBV infection, and an epidemiologic survey in 2020 showed that the HBs Ag carrier rate in the general population was 4.57%, with about 70 million cases of chronic HBV infection.[79,80] Hepatitis B is highly contagious and is mainly transmitted through mother-to-child, blood and sexual contact, with mother-to-child transmission dominating in China, and adults mainly transmitted through blood and sexual contact.

Tumorigenic Mechanisms of HBV Infection

Persistent HBV infection is a major risk factor for HCC, a cancer typically associated with chronic inflammation. HBV may contribute to the development of HCC through two major mechanisms: (1) integration of HBV into the DNA of host cells and mutation of the viral genome in the DNA of host cells, which may lead to altered expression of important host genes; and (2) expression of proteins such as p53, Fas-like factor binding protein 3, and integrin β1, which may have a direct effect on cellular function, thereby promoting tumorigenesis. HBV-expressed proteins such as p53, insulin-like factor binding protein 3, Fas-associated protein structural domains, and integrin β1 may have a direct role for cellular function, thereby promoting tumorigenesis. Hepatitis B virus X protein (HBx) is a functional core protein of HBV, which can cause viral replication through protein-protein interactions, thereby altering the expression of host genes to the extent that it promotes the proliferation of tumor cells. SNHG 12 (small nuclear kernel RNA host gene 12) is a tumor-associated, long-stranded, non-coding RNA. In hepatocellular carcinoma, the Notch signaling pathway plays an important role in tumor development. Notch signaling pathway plays an important role in the development of hepatocellular carcinoma, and inhibition of SNHG12 can downregulate Notch1 signaling pathway to affect cell proliferation, migration, and invasion. Wu et al mimicked the natural infection with HBV by establishing a mouse model with stable expression of HBx, and found that HBx affects the cell cycle through upregulation of SNHG 12 and promotes the upregulation of Notch 1, and plays an important role.[81] The pathogenic mechanism of HBV is shown in Figure 4.

Neoplastic Diseases Associated with HBV Infection

Previous studies have confirmed that HBV infection is closely related to the occurrence of HCC. Over the past 30 years, research on the correlation between HBV infection and extrahepatic tumor incidence has continued to emerge. The earliest study on the correlation between HBV and extrahepatic tumors was reported in 1994,[82,83] when Galun et al first

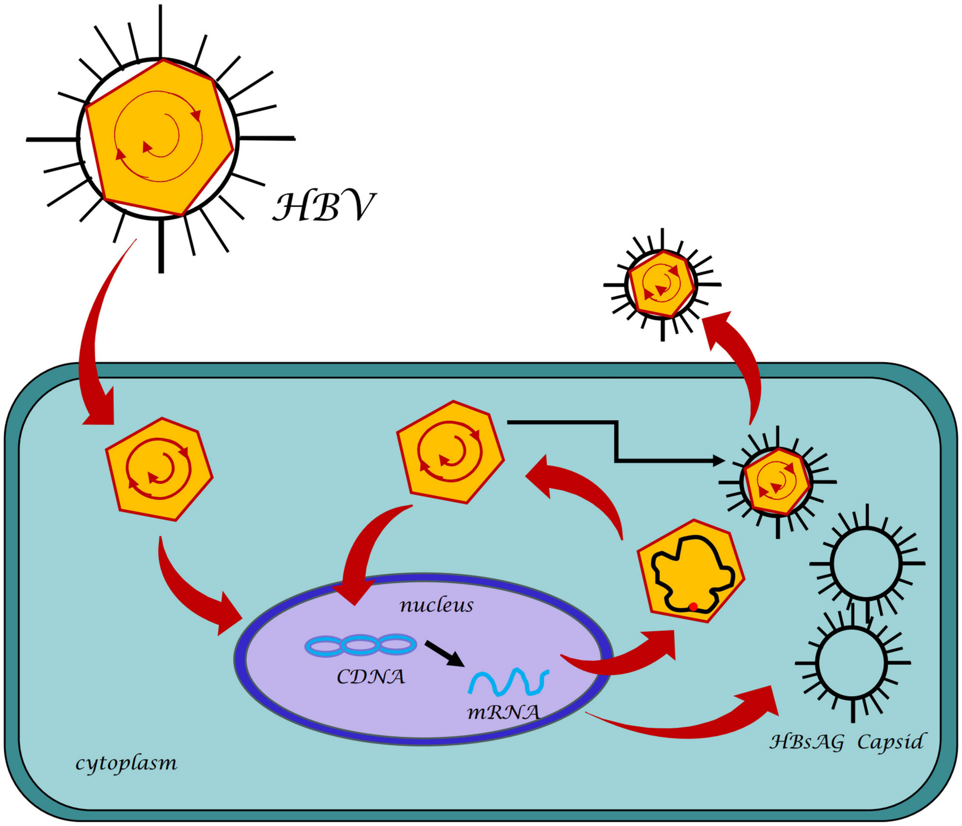

Figure 4 Pathogenic Mechanism of HBV.

used immunohistochemistry to detect HBsAg in the bone marrow cells of patients with leukemia and in the endothelial cells of lymphoma patients, suggesting a correlation between HBV infection and extrahepatic tumors. Additionally, HBV infection has also been shown to correlate with the occurrence of tumors in digestive organs such as the bile ducts, pancreas, and stomach, which are anatomically close to the liver.[84–86] Furthermore, a study involving 95,034 patients with non-hepatic cell malignancies and 118,891 non-cancer patients found, through conditional logistic regression analysis, that HBV infection might be related to gynecological malignancies such as cervical cancer, endometrial cancer, and ovarian cancer.[87,88] Cao et al[89] conducted a case-control study on 711 patients with nasopharyngeal carcinoma and found a high correlation between HBV infection and the incidence of nasopharyngeal carcinoma.

Polyomavirus

Polyomaviruses are small, non-enveloped DNA viruses with a circular double-stranded genome of approximately 5000 base pairs, encoding early proteins (large T and small t antigens) and late structural proteins (VP1, VP2, VP3).[90,91] Among them, BK polyomavirus (BKV) and simian virus 40 (SV40) have garnered significant attention due to their potential roles in human carcinogenesis. BKV commonly establishes latent infection in the urinary tract, while SV40, originally identified in monkeys, has been detected in several human cancers.[92,93] Their oncogenic potential is largely attributed to the expression of viral T antigens, which interact with host tumor suppressor proteins such as p53 and retinoblastoma (Rb), thereby dysregulating cell cycle control and promoting genomic instability.

Tumorigenic Mechanisms of Polyomavirus Infection

Emerging evidence highlights the involvement of polyomaviruses in human tumorigenesis through both direct and indirect mechanisms. A critical oncogenic process involves the truncation of large T antigen (LT), induced by host cytidine deaminases such as APOBEC and AID (activation-induced cytidine deaminase). A recent study demonstrated that the SV40 enhancer possesses strong somatic hypermutation targeting activity, facilitating AID-induced mutations in the LT coding region across multiple cell types, including B cells and kidney cells. These mutations lead to LT truncation, which enhances its transforming activity—a mechanism analogous to that observed in Merkel cell polyomavirus (MCPyV), where truncated LT promotes carcinogenesis.[94]

Furthermore, persistent expression of viral T antigens may drive malignant transformation even after the control of primary infection. A novel clinical case revealed that in a kidney-pancreas transplant recipient, BKV nephropathy was followed—after a significant latency period—by the development of collecting duct carcinoma. Although systemic BKV replication was undetectable at the time of cancer diagnosis, viral T antigen was persistently expressed specifically within tumor cells, suggesting a direct oncogenic role of the virus through continuous protein expression rather than active viral replication.[95] These findings underscore the importance of long-term clinical vigilance even after virological clearance in immunocompromised patients.

Additional mechanisms include the capacity of T antigens to disrupt DNA repair pathways, induce chromosomal instability, and modulate host immune responses, fostering a tumor-permissive microenvironment. The pathogenic mechanism of polyomavirus is shown in Figure 5.

Neoplastic Diseases Associated with Polyomavirus Infection

Although best known for their roles in renal and urinary tract diseases in immunocompromised individuals, polyomaviruses have been implicated in a range of malignancies. BKV has been associated with renal cell carcinoma and urothelial carcinomas, particularly in transplant recipients. SV40 has been detected in lymphomas, mesotheliomas, and brain tumors, although its broader oncogenic significance in humans remains under investigation. The recent clinical association between cleared BKV infection and subsequent renal carcinoma highlights the potential for delayed oncogenesis long after initial infection, suggesting that the oncogenic risk of polyomaviruses may extend beyond traditionally recognized contexts.

Moreover, molecular studies have revealed a novel mutagenic pathway linking SV40 infection to lymphomagenesis through AID-mediated LT truncation, proposing a broader relevance of polyomaviruses in hematopoietic malignancies. These insights call for further large-scale epidemiological and mechanistic studies to clarify the spectrum of cancers linked to polyomaviruses and to develop targeted surveillance strategies for high-risk populations.

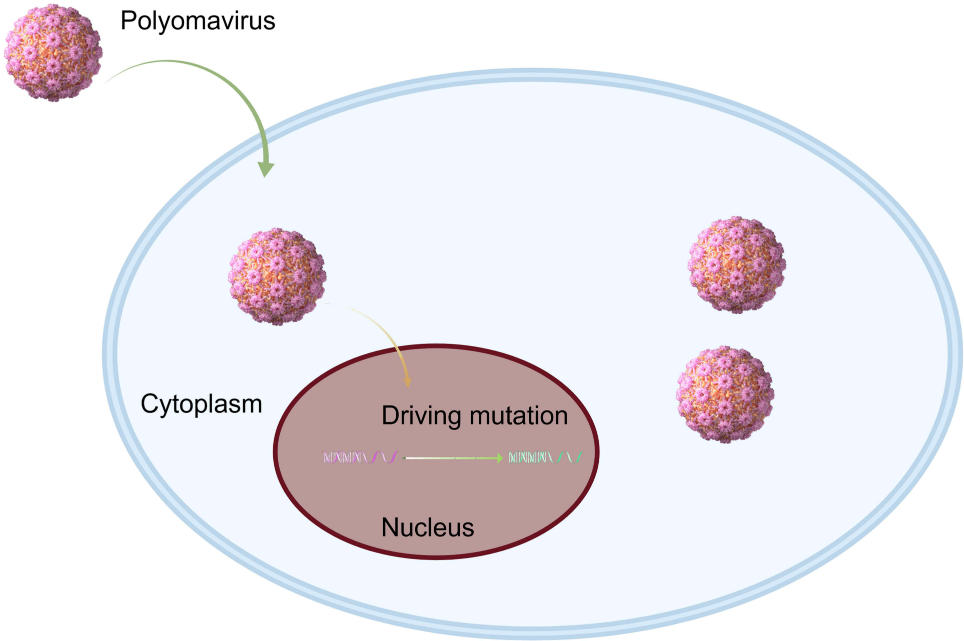

Figure 5 Pathogenic Mechanism of polyomavirus.

RNA Tumour Virus

RNA viruses are a class of viruses with RNA as their genetic material, and usually their nucleic acids are single-stranded or double-stranded. Single-stranded RNA viruses can be classified into positively translated, negatively translated, and double-translated RNA viruses according to the translation. positively-translated RNA viruses are similar to mRNAs, and can be directly translated into proteins by the ribosomes; negatively-translated RNA viruses need the action of RNA polymerase to synthesize positively-translated RNAs complementary to themselves, and then translate proteins using these RNAs as mRNA. RNA viruses have two modes of replication: self-replicating and reverse transcription, and the human tumor-related RNA oncoviruses, human T-lymphotropic virus type I and human acquired immunodeficiency virus, are both reverse transcription viruses, while the hepatitis C virus is a single-stranded positive-stranded RNA virus. These RNA tumor viruses all consist of a core and envelope, and their genomes all have regions encoding structural genes and regions encoding non-structural proteins, and the proteins encoded by these genes play an important role in the replication, assembly and release of the viruses. When retroviruses infect the organism, they reverse transcribe into double-stranded DNA under the action of reverse transcriptase, and then integrate into the host genome, continuously expressing viral growth-regulating proteins and thus causing tumorigenesis.

Human T-Cell Lymphotropic Virus Type 1 (HTLV-1)

HTLV-1 was isolated in the early 1980s from T-cell lines derived from patients with cutaneous T-cell lymphoma and adult T-cell leukemia, making it the first retrovirus found to be associated with human tumors.[96] The full 8.5-kbp genome of HTLV-1 includes the structural genes gag, pol, pro, env, and the pX region. The pX region contains sequences of proteins involved in viral infection and pathogenicity of the virus and sequences of the viral regulatory and auxiliary proteins Tax, Rex, p12, p13, p30, p21, and the HTLV-1 bZIP factor (HBZ).[97] The main routes of transmission of HTLV-1 are adjuvant blood products, sexual and intrafamilial, with intrafamilial transmission occurring horizontally between husband and wife and vertically between parents and children.

Tumorigenic Mechanism of HTLV-1 Infection

There are 15 to 20 million HTLV-1-infected people in the world, but more than 95% remain asymptomatically infected[98] emphasizing the role of the immune system in controlling infection. In vivo HTLV-1 predominantly infects CD4^{+}T cells, which are the key cells for triggering and establishing an adaptive immune response. The oncoproteins Tax and HBZ play key roles in HTLV-1 infection and tumorigenesis. Tumor disease occurs in transgenic mice expressing either Tax or HBZ, suggesting oncogene function.[99] Tax is a viral transcriptional activator that contacts oncogenic signaling pathways, promotes cell cycle progression, and contributes to HTLV-1-induced tumorigenesis. In addition, Tax mainly targets the IκB kinase complex in the cytoplasm and inhibits the autophagy pathway, leading to sustained activation of NF-κB and up-regulation of the expression of its responsive genes, which is critical for T-cell survival and cell-cycle progression.[100] In addition, it has been demonstrated that the expression of HBZ is more prevalent compared to Tax, and HBV is not only found in asymptomatically infected individuals and in the HTLV-1-associated myelopathy/tropical spastic paralysis, but also in the nuclei of tumor cells from leukemia patients, and that HBZ subcellular localization may be a prognostic marker for HTLV-disease progression.[101,102] The pathogenic mechanism of HTLV-1 is shown in Figure 6.

Neoplastic Diseases Associated with HTLV-1 Infection

HTLV-1 not only serves as the etiological agent of adult T-cell leukemia/lymphoma (ATL) but also can lead to HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a lethal chronic inflammatory neurological disease. Recent studies have found associations between HTLV-1 infection and some typical autoimmune diseases, such as uveitis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome. This may result from the formation of shared antigens between the host's tissues and viral proteins, leading to autoimmune attacks and subsequent pathogenesis.[103,104] The earliest case report, dating back to 1990,[105] detected HTLV-1 antigen in the serum and synovial lymphocytes of a 57-year-old woman with rheumatoid arthritis.

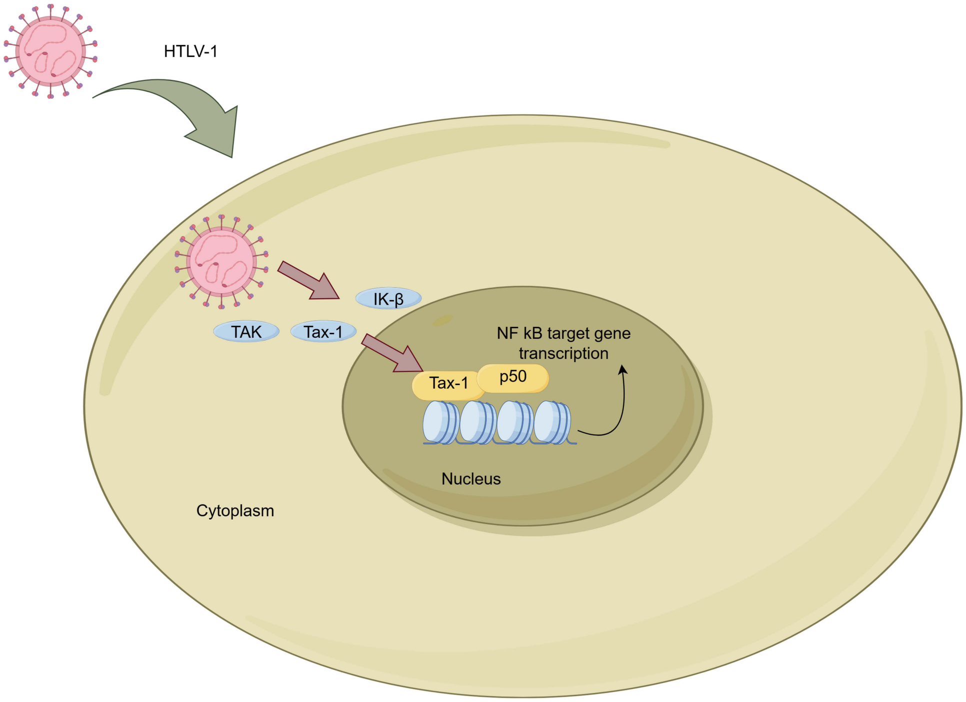

Figure 6 Pathogenic Mechanism of HTLV-1.

Hepatitis C Virus (HCV)

HCV is an enveloped, single-stranded, linear RNA virus with a genome length of 9.6 kbp, comprising structural and non-structural protein regions. The structural protein genes include core protein, envelope glycoprotein genes E1 and E2; non-structural protein genes include P7, NS1, NS2, NS3, NS4A, NS5A, and NS5B. These proteins play roles in virus replication, assembly, and release.[106] A key characteristic of the HCV genome is its high degree of polymorphism and variability. Currently, HCV can be classified into six genotypes (1–6), each with differences in pathogenicity, response to interferon, and disease progression.

Tumorigenic Mechanisms of HCV Infection

HCV, an RNA virus, cannot directly integrate into the host cell genome. It must alter genetic and epigenetic mechanisms through complex interactions between viral proteins and cells, leading to the inactivation of oncogenes, tumor suppressor genes, and dysregulation of multiple signaling pathways, resulting in inflammation, fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC). Activation of the virus's survival and growth pathways is mediated by core protein, envelope glycoprotein E2, non-structural proteins NS2, NS3, NS4A, NS5A, and NS5B. NS5A, a phosphorylated protein, interacts with various host proteins, playing a crucial role in viral replication; NS5B possesses RNA-dependent RNA polymerase activity, participating in HCV genome replication. Core protein, envelope glycoprotein E2, non-structural proteins NS3, and NS5A can interact with multiple proteins in the RAF/MAPK/ERK pathway to promote cell proliferation.[107] NS5A binds to tumor suppressor factor pTEN, inactivating it, and promotes tumor cell proliferation and growth through the PI3K/Akt pathway.[108] TIPE2, a newly discovered immune negative regulator, plays a crucial role in regulating inflammation, tumor development, and immune homeostasis. NS5A can interact specifically with TIPE2 and induce its degradation,[109] promoting tumor development, suggesting that TIPE2 may be a novel target for treating HCV-induced HCC. Recent studies have shown that exosomes can promote HCV infection and mediate immune responses to mask viral particles and RNA. Exosomes can serve as biomarkers for the severity of virus infection and treatment efficacy.[110] The pathogenic mechanism of HCV is shown in Figure 7.

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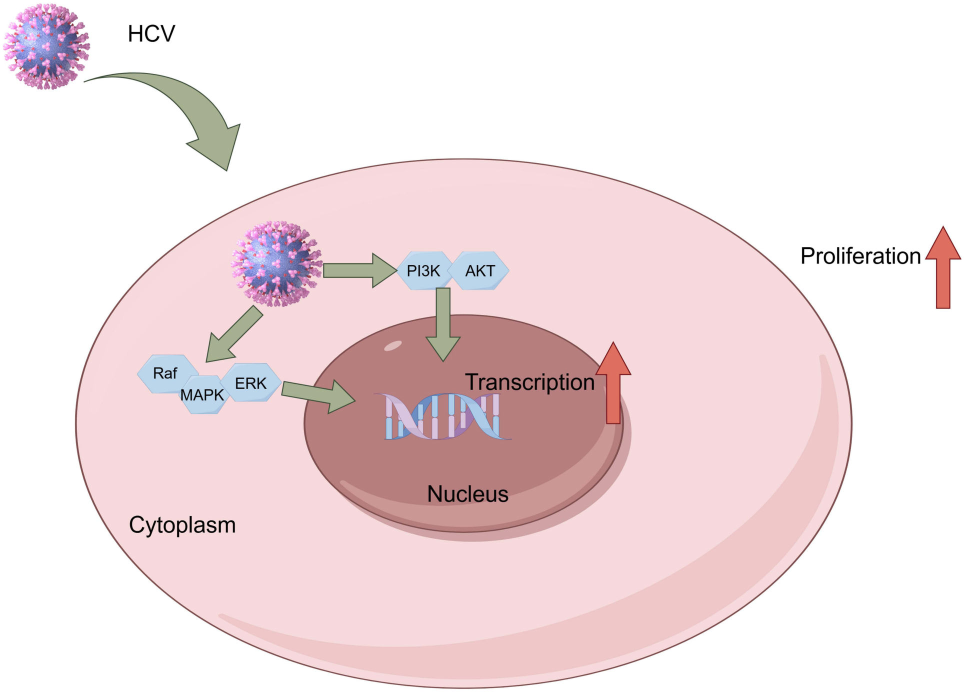

Figure 7 Pathogenic Mechanism of HCV.

Neoplastic Diseases Associated with HCV Infection

HBV-related HCC is common in developing countries, while HCV-induced HCC is more prevalent in developed countries. Notably, infection with HCV genotype 3 is associated with an 80% higher risk (adjusted HR = 1.8) of developing HCC compared to genotype 1.[111] Additionally, a retrospective cohort study comparing 145,210 HCV-infected patients with 3,948,826 non-infected individuals found a relative risk for developing cholangiocarcinoma, pancreatic cancer, and non-Hodgkin lymphoma of 68.67, 2.79, and 3.59, respectively. These results suggest that chronic HCV infection may increase the incidence of cholangiocarcinoma, pancreatic cancer, and non-Hodgkin lymphoma.[111,112]

Human Acquired Immunodeficiency Virus (HIV)

HIV was first discovered in the United States in 1981 and belongs to the human lentivirus group of retroviruses. It is a spherical particle with a diameter of 100–120nm, consisting of a core and an envelope. The core is composed of capsid protein p24, containing two identical single-stranded positive-sense RNA genomes, nucleocapsid protein NC, and enzymes necessary for virus replication. The outermost layer of the virus is the envelope, which contains glycoproteins gp120 and gp41. Below the envelope structure is the matrix protein p17, forming the viral capsid. The HIV genome is approximately 9.7kb in length and consists of three structural genes (gag, pol, and env), two regulatory genes (tat, rev), and four accessory genes (nef, vpr, vif, vpu/vpx). HIV is a highly mutable virus, with varying degrees of mutation in each gene, with the env gene having the highest mutation rate. HIV is divided into HIV-1 and HIV-2 types, with HIV-1 being the predominant strain in China. The sources of HIV transmission are HIV-infected individuals and AIDS patients, primarily through sexual contact, blood and blood products, and mother-to-child transmission.

Tumorigenic Mechanisms of HIV Infection

After entering the human body, HIV primarily infects CD4$^+$T cells.[113] The viral envelope protein gp120 specifically binds to the CD4 receptor on the surface of lymphocytes, causing a conformational change in gp120, exposing binding sites for co-receptors on the T lymphocyte membrane. Upon further binding with co-receptors, gp41 undergoes conformational changes, leading to membrane fusion under the action of relevant factors, allowing HIV entry into host cells. Within host cells, the virus utilizes proteases to hydrolyze capsid proteins, reverse transcribes viral RNA into DNA,

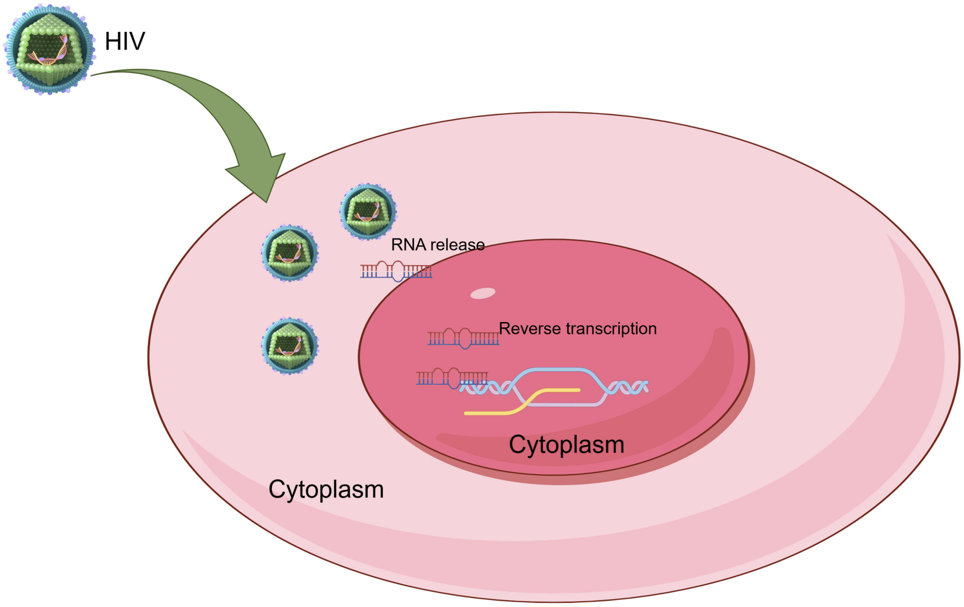

Figure 8 Pathogenic Mechanism of HIV.

integrates into the host cell's DNA for transcription and expression under the action of integrase, assembles into progeny HIV particles, and releases from host cells via budding, resulting in host cell lysis and death. Infection with HIV in the human body manifests as a gradual decrease in CD4$^+$T cells, ultimately leading to immune deficiency. Immune suppression and persistent viral infection lead to chronic inflammation. Additionally, individuals infected with the human immunodeficiency virus are more prone to cancer risk behaviors such as male-to-male sexual behavior, intravenous drug use, heavy alcohol consumption, and smoking. They are also more susceptible to co-infection with other oncogenic viruses (Epstein-Barr virus, human herpesvirus, hepatitis B and C viruses), exacerbating immune system dysregulation and increasing the risk of cancer occurrence.[114,115] The pathogenic mechanism of HIV is shown in Figure 8.

Neoplastic Diseases Associated with HIV Infection

The human immunodeficiency virus (HIV) increases the risk of various malignancies by impairing the body's immune function, particularly following the widespread use of antiretroviral therapy (ART) for HIV/AIDS. While the mortality rate of HIV-infected/AIDS patients has significantly decreased with the prolonged lifespan due to ART, the increased longevity also raises the likelihood of co-infection with other oncogenic viruses. Consequently, the proportion of HIV-infected/AIDS patients developing malignancies has notably increased,[116] with malignancies increasingly becoming the leading cause of death in this population. HIV-associated malignancies can be categorized into AIDS-related and non-AIDS-related tumors.[117,118] AIDS-related malignancies include Kaposi's sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer, while non-AIDS-related tumors comprise lung cancer, liver cancer, anal cancer, prostate cancer, skin cancer, colorectal cancer, and Hodgkin lymphoma. Non-AIDS-related tumors predominate among HIV-infected/AIDS patients with malignancies, with a higher incidence of lymphoma in HIV-associated malignancies.

Therapeutic and Preventive Strategies for Viral-Induced Cancers

Significant progress has been made in developing targeted therapies and preventive measures against virus-associated cancers. Vaccination remains the most effective preventive strategy, with prophylactic vaccines against HPV and HBV demonstrating remarkable success in reducing the incidence of related cancers.[119,120] Therapeutically, immune-based approaches such as immune checkpoint inhibitors and adoptive T-cell therapy have shown promising results in treating EBV-associated lymphomas and HPV-positive cancers.[121,122] For instance, inhibitors of PD-1/PD-L1 have been approved for use in virus-related malignancies including HCC and classical Hodgkin lymphoma.[123,124] Recent advances also include the development of therapeutic vaccines targeting viral oncoproteins, such as those against HPV E6/E7 proteins,[125] which are currently in clinical trials. Additionally, novel molecular approaches including CRISPR-based gene editing and small molecule inhibitors targeting viral-host interaction interfaces offer promising avenues for precision therapy.[126,127] These advancements not only improve clinical outcomes but also highlight the importance of understanding viral oncogenesis in developing effective interventions.

Conclusions

This review elucidates the roles of DNA and RNA tumor viruses in human carcinogenesis, highlighting both established and emerging mechanisms of viral oncogenesis (Table 2). Beyond summarizing viral-host interactions, this work offers unique insights into several underappreciated aspects of tumor virology. Specifically, we emphasize the significance of

Table 2 Comparative Assessment of Major Oncogenic Pathways Across Tumor Viruses

Virus	**Key Oncogenic Pathway / Mechanism**	**Relative Contribution (High/ Medium/Low)**	**Key Supporting Evidence (Example)**
HPV	E6-mediated degradation of p53	High	Found in >90% of HPV-associated cancers; essential for immortalization.[38]
	E7-mediated inactivation of pRb	High	Disrupts cell cycle control; necessary for transformation.[29]
HBV	HBx protein activation of signaling (eg, SNHG12-Notch1)	High	HBx is expressed in integrated HBV DNA in most HCCs; drives proliferation in models.[81]
	Viral DNA integration causing genomic instability	Medium	Common but not always driver; can disrupt tumor suppressor genes.[81]
EBV	LMP1-mediated constitutive NF-κB activation	High	LMP1 is considered the primary oncoprotein; mimics active CD40 signaling.[40]
	EBNA2-mediated modulation of host transcription	High	Reprograms B cell gene expression, promoting growth and survival.[41]
KSHV	vFLIP inhibition of apoptosis	High	Essential for survival of latently infected endothelial cells in KS.[59]
	LANA-mediated inhibition of p53 and pRb	High	LANA is expressed in all KSHV-associated tumors; crucial for latency and oncogenesis.[58]
MCPyV	Truncated LT antigen loss of replication function	High	>80% of MCC tumors harbor viruses with specific LT truncations, a hallmark of viral-driven transformation.[94]
Polyomavirus (SV40/BKV/JCV)	Large T antigen inactivation of p53 and pRb	High	Primary mechanism demonstrated in transgenic mouse models showing tumor development.[15,16]
	AID/APOBEC-mediated LT truncation (Emerging)	To be determined	Demonstrated in human B cells and kidney cells; potential mechanism for enhanced transformation.[94]
HCV	NS5A-mediated immune evasion (eg, TIPE2 degradation)	High (for immune persistence)	NS5A is central to viral replication and modulating host responses; promotes survival.[109]
	Core protein-induced oxidative stress and inflammation	High	Chronic inflammation is a hallmark of HCV infection and a major driver of HCC.[107,108]
HTLV-1	Tax-driven NF-κB activation and genomic instability	High (in early transformation)	Tax is a potent transactivator but often silenced in full-blown ATL via immune editing.[100]
	HBZ RNA-driven proliferation and immune suppression	High (in maintained disease)	HBZ is consistently expressed in ATL cells and promotes oncogenesis.[99]
HIV	Immunosuppression leading to loss of viral surveillance	High	Sharp increase in risk for AIDS-defining cancers.[113]
	Chronic inflammation and co-infection with other oncogenic viruses	High	Creates a permissive environment for virus-driven cancers (eg, HPV, HBV, HCV, KSHV).[114,115]

AID-induced truncations in polyomavirus T antigens as a novel oncogenic mechanism, and detail the roles of HBV-HBx–SNHG12–Notch1 axis in hepatocellular carcinoma and HCV-NS5A–mediated TIPE2 degradation in immune evasion.

These findings suggest new therapeutic opportunities, such as targeting the SNHG12–Notch1 pathway or restoring TIPE2 function in virus-related cancers. Furthermore, our analysis supports the expansion of vaccination programs and development of targeted interventions against polyomaviruses.

Future studies should prioritize high-throughput identification of key virus–host interaction nodes, development of pathway-specific inhibitors, and large-scale clinical studies to clarify the molecular evolution of precancerous lesions. Ultimately, interdisciplinary efforts are essential to advance precision medicine in viral oncology and reduce the global burden of virus-associated cancers.

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Disclosure

The authors report no conflicts of interest in this work.

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