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Review

Pathogenesis of Oncoviruses: A Systemic Review

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Viral oncology is focused on understanding the relationship between cancer and viruses, which are known to play a role in the development of certain types of cancer. Approximately 15-20% of human cancers are believed to be caused by oncogenic viruses, and as a result, there is significant interest in understanding how these viruses contribute to cancer development. There are several viruses that have been linked to cancer, including human papillomavirus, hepatitis B and C virus, Epstein-Barr virus, human T-cell lymphotropic virus type 1, Kaposi's sarcoma-associated herpesvirus, and Merkel cell polyomavirus. Each of these viruses is associated with different types of cancer, and the mechanisms by which they contribute to cancer development are diverse. This article discusses these mechanisms as well as current and future strategies for preventing and treating virus-associated cancers with the goal of presenting a thorough review of the current state of knowledge in viral oncology and to highlight the importance of continued research in this field.

Keywords: **Oncogenesis, cancer, virology, HPV, oncoviruses**

Introduction

Viral oncology is a rapidly growing field that is focused on understanding the relationship between viruses and cancer. Worldwide, cancer is the leading cause of death and viruses are known to contribute in the growth of certain types of cancer. Approximately 15–20% of human cancers are believed to be caused by oncogenic viruses [1]. The worldwide impact of cancer caused by infectious agents is on the rise for various reasons, including poor hygiene, and sexual contact during intercourse. The most prevalent cause of cancer is the bacterium *Helicobacter pylori*, which is responsible for various types of cancers followed by human papillomavirus (HPV) [2, 3].

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One of the most well-known examples of a virus that can cause cancer is human papillomavirus. A common sexually transmitted pathogen HPV that can cause cervical cancer, as well as other types of cancer such as anal, oropharyngeal, vaginal, and vulvar cancer [4]. In fact, the Centers for Disease Control and Prevention state, HPV associated cancer are responsible for more than 47,199 cases each year [5]. Other viruses that have been linked to cancer include the hepatitis B and C viruses (HBV and HCV), which are linked with liver cancer, and the Epstein-Barr virus, which is linked with certain types of lymphoma [6]. The first oncovirus was discovered in 1964 by M. A. Epstein in a case of Burkitt's lymphoma. Initially, it was noted for its resemblance to the Herpes simplex virus and was later named the Epstein-Bar virus [7].

Recent research has begun to shed light on the mechanisms by which these viruses contribute to cancer

development. For example, it is known that certain strains of HPV can integrate into the DNA of host cells, resulting in the suppression of tumor suppressor genes and the stimulation of oncogenes. This can lead to uncontrolled cell growth and the formation of a tumor [8]. Similarly, the into HBV and HCV are known to lead to chronic inflammation and damage to the liver, which can ultimately lead to liver cancer [9, 10].

In terms of prevention and treatment, there are two different strategies to tackle these infections. One of the most promising strategies is the development of vaccines. For example, for preventing HPV infections, the HPV vaccine is very successful, and has been demonstrated to significantly lower the risk of cervical cancer [11, 12]. Similarly, the hepatitis B vaccine can help prevent HBV infections, and thus reduce the risk of liver cancer. Second most promising strategy is the use of anti-viral therapies to target the virus directly, or to target the cancer cells that have been infected with the virus [13]. All of these viruses have unique oncogenes and proteins. These oncogenes can play a part in the growth and progression of tumor [14]. There is total seven viruses that can cause different kinds of cancers [15].

In this article, we will delve deeper into the current state of research in viral oncology and provide an overview of the seven types of viruses as depicted in Fig. 1 that have been linked to cancer, the mechanisms by which these viruses contribute to cancer development, and current and future strategies for preventing and treating viral-associated cancers. We will also discuss the challenges and limitations of this field and what is needed to further our knowledge of the intricate interaction between cancer and viruses. The goal of this article is to provide a thorough and current review of the current state of knowledge in viral oncology and to highlight the importance of continued research in this field.

Fig. 1. Graphical representation of Oncogenic viruses.

Global impact of carcinogenic agents

The International Agency for Research on Cancer (IARC) has identified 11 agents that have been linked to causing cancer. These agents include one bacterium, *H. pylori*, and three parasites, *Schistosoma haematobium*, *Opisthorchis viverrine*, and *Clonorchis sinensis*. The remaining seven agents are viruses, including HBV and HCV, Kaposi's sarcoma herpesvirus (KSHV), also known as human herpes type 8 virus, Epstein bar virus, human T-cell lymphotropic virus type 1 (HTLV-1), Merkel cell polyomavirus and HPV [15, 16]. HPV has both low- and high-risk types, with high-risk types including 18, 39, 35, 31, 35, 16, 51, 56, 58, 52, 66, 59, and 33 being the primary cause of cancer. Types 16 and 18 of this group of high-risk HPV are in charge of 70% of cervical cancer cases globally [17]. Low-risk HPV types such as 11, 42, 44, 6, 43, 53, 44, 61, 54, 81, and 72 are not that prominent [18].

From 2012 to 2018, the impact of carcinogenic agents is on rise. The total number of cases in case of HPV in 2012 was 640,000 and it was 690,000 in 2018 [2, 15]. Similar index rate was observed in other carcinogenic agents. Table 1 depicts the cancers caused by viruses along with their oncogenes or proteins.

HBV and HBC

The HBV is a small virus that belongs to the *Hepadnaviridae* family, partially double-stranded DNA virus having characteristics resembling those of retroviruses [30, 31]. The genome of HBV is approximately 3.2 kilobase pairs in size and is depicted as a circular DNA structure. HBV have around 8 genotypes. The virion of HBV is referred to as the Dane particle along with the core antigens [32–34].

HBV affects the liver and can cause both acute and chronic diseases affecting more than 350 million people

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Table 1. Tabular depiction of oncoviruses and their associated diseases.

Pathogen	Cancer disease	Oncogene/protein	Vaccine	IARC Classification	References
Hepatitis B	Hepatocellular carcinoma	*p*53, HBx gene	Present	1	[13, 19]
Hepatitis C	Non-Hodgkin lymphoma and Hepatocellular carcinoma	186-gene, core, E1, E2, NS3, and NS5A proteins	Nil	1	[20, 21]
KSHV	Kaposi Sarcoma, Primary effusion lymphoma	vFLIP protein	Nil	1	[22, 23, 24]
HTLV-1	Adult T-cell leukemia/ lymphoma (ATL)	tax and hbz genes	Nil	1	[25]
Merkel cell polyomavirus	Merkel cell carcinoma (MCC)	small T-antigen [ST], large T-antigen [LT] and ALTO [alternate frame of the large T ORF] and two viral coat proteins, VP1 and VP2	Nil	1	[26]
Epstein bar virus	Burkitt's lymphoma, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, gastric carcinoma and nasopharyngeal	HLA-A/B, HLA-region	Nil	1	[27]
HPV [High Risk]	Cervical, anogenital, head and neck carcinoma	E6 and E7 gene	Present	1	[28, 29]

worldwide [35]. The contact with infected bodily fluids is responsible for the spread of virus, such as semen, blood, and vaginal secretion, and can also be transmitted through contaminated practices such as tattooing and body piercing [36]. In some individuals, acute hepatitis B infection can resolve on its own within a few months, but in others it can progress to chronic infection, which can last a lifetime and lead to serious health complications, including liver cirrhosis and hepatocellular carcinoma (HCC), which is a type of liver cancer [37, 38].

Studies have shown that chronic infection with hepatitis B increases the risk of developing HCC. This is because the persistent presence of the virus in the liver can lead to chronic inflammation and damage to liver cells, which can eventually lead to the formation of cancerous cells [39]. The risk for HCC is highest in individuals with chronic hepatitis B infection who also have cirrhosis, as the liver damage and scarring associated with cirrhosis can increase the likelihood of cancer development [40]. The estimated HCC death toll is more than 0.5 million per year and considered as the 2nd cause of death due to cancer [41, 42].

On the other hand, HCV is a blood-borne virus that primarily infects liver cells, causing liver inflammation and tissue damage. It is characterized as a member of the *Flaviviridae* family and the *Hepacivirus* genus, characterized as a small enveloped single stranded positive-sense RNA virus [43]. HCV is highly infectious and can be transmitted through contaminated blood, such as through sharing needles or receiving a transfusion before widespread screening of the blood supply was introduced [44]. Chronic HCV infection is a major global contributor to liver-related morbidity and mortality and can induce catastrophic liver conditions such liver and cirrhosis cancer [45]. The course of HCV infection is highly variable, and some infected individuals may remain asymptomatic for many years, while others may progress to liver disease [46].

In conclusion, hepatitis B and C are serious viral infections that may be able to cause both acute and chronic diseases, possessing a high potential for liver cancer development in individuals with chronic infections.

Pathogenesis

HBV and HCV trigger the development of HCC in a context of inflammation and regeneration that originates from long-term liver damage, indicating that the base of HCC is linked to the immune system [47]. The HBV and HCV proteins change the way host genes are expressed and the cellular characteristics, which are

hallmark signs of cancer. These modifications cause tissue invasion, angiogenesis, metastasis, growth-factor independent cell division, altered energy metabolism, resistance to growth inhibition, and resistance to cell death despite persistent immune response and treatment [48]. Chronic inflammation also causes genetic instability in tumor cells. HBV contributes to liver cancer by expressing the HBx protein, and HCV's contribution involves the core protein and non-structural proteins NS3 and NS5A. Changes in host gene expression that support tumor growth also seem to support virus replication and protect virus-infected cells from immune damage. The development of liver cancer doesn't appear to benefit the virus and often leads to the death of the host [49].

Virus persistence, the long-term existence of HBV and HCV in infected cells, is crucial in the development of liver cancer. HBV DNA persists as an episome in the form of a minichromosome in cell nuclei, and integration of HBx and truncated S/pre-S sequences into host DNA can lead to tumor growth [50]. HCV, on the other hand, persists as an endoplasmic reticulum (ER)-associated episome without integration. The survival and growth of virus-infected cells favored by the viruses contributes to liver cancer progression such as chronic liver disease (CLD). Co-infections of both viruses in a single patient seem to accelerate the pathogenesis of liver cancer through common mechanisms that cause oxidative stress and production of harmful cytokines. In addition, variations in the virus genome can also impact the replication and interaction of viruses, particularly in patients infected with both HBV and HCV [49]. The progression of HBV and HCV induced cancer is expressed in Fig. 2 [51].

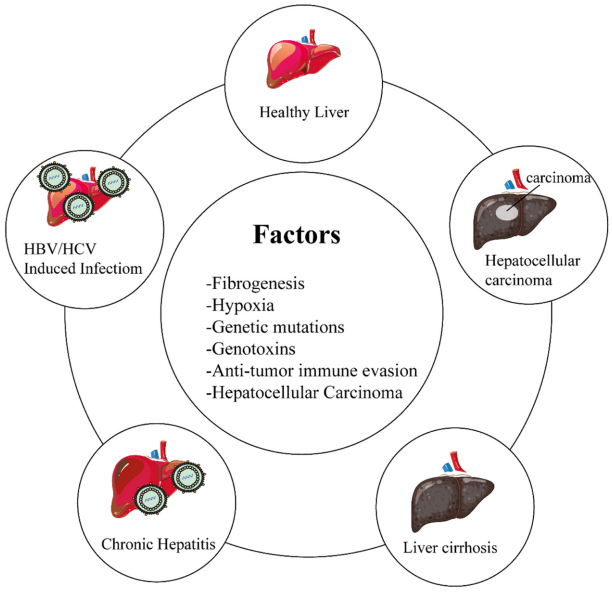

Fig. 2. The progression of HBV and HCV induced Hepatocellular carcinoma.

However, the impact of cancer is amplified when a secondary infection with HIV is present in patients already infected with either HBV or HCV. The severity of the disease and its progression to chronicity is affected by various factors, like viral load, the age of infection, and the presence of co-infections with other liver pathogens and conditions [52].

Treatment

There are ongoing trials to assess the effectiveness of immunotherapy and vaccinations in treating carcinoma caused by HBV and HCV. Despite these efforts, the use of vaccines to prevent HCC remains limited. One potential reason for this low efficacy is that the immune system may develop tolerance to self-antigens (such as TAA), which hinders the development of a strong antitumor immune response. The most effective way to prevent the development of cancer is to treat the infection in its early stages. Fortunately, vaccines for both HBV and HCV are available to both prevent and cure these diseases [53].

Kaposi's Sarcoma Herpesvirus

Those with a weakened immune system, such as those with untreated HIV, are susceptible to infection by the Kaposi's sarcoma herpesvirus, leading to the development of neoplasms [54]. Herpesviruses are composed of a double-stranded DNA genome surrounded by a viral capsid protein, a tegument layer, and a lipid envelope featuring eight distinct glycoproteins. These viruses cause primary infections that establish lifelong latent infections in the host with periodic reactivations. KSHV, also known as human herpesvirus-8, belongs to the family of 2-lymphotropic-oncogenic herpesviruses and is linked to primary effusion lymphoma (PEL), multicentric Castleman's disease (MCD), and Kaposi's sarcoma. It is the newest member of the human herpesvirus family and is connected to the Rhesus monkey rhadinovirus, herpesvirus saimiri, and the Epstein-Barr virus [55].

Pathogenesis

Kaposi's Sarcoma (KS) is caused by changes in cell shape, growth rate, metabolism, gene expression and lifespan brought on by KSHV infection of endothelial cells or hematopoietic progenitors. The carcinogenic characteristics of KSHV are demonstrated by the induction of pro-angiogenic molecules such as members of the VEGF-VEGFR family and angiogenin [56]. *In vitro* studies suggest that KSHV infection of endothelial cells results in morphological changes and extended lifespan but does not cause full neoplastic transformation. The development of KS requires cofactors including drug-induced immunosuppression or HIV. Although KSHV is lpresent in most KS spindle cells, only a small proportion undergo lytic replication, resulting in virus production and cell lysis involving viral FLICE inhibitory protein (vFLIP) and viral cyclin (vcyclin). The herpes viral paradigm of latent or lytic infection may not limit the production of KSHV genes, including early lytic genes, as lytic genes can be produced without completing the lytic cycle. This has consequences for comprehending how latent and lytic gene-expressing cells contribute to the pathogenesis of KS [54]. Unfortunately, currently, there is no available vaccine to treat induced Carcinoma and KSHV infection.

Treatment

The Food and Drug Administration (FDA) has not yet approved any treatment for KSHV. KSHV-MCD has been treated with a number of cytotoxic chemotherapies, including doxorubicin, vincristine, vinblastine, cyclophosphamide, and etoposide, all of which have had clinical activity in B-cell lymphomas. Chemotherapy by itself, though, is not very successful. The reported survival with these chemotherapies, either independently or in combination, was dismal in one analysis between 1985 and 2006, with an average survival rate of 12 months [57].

Antiretroviral therapy (ART) is recommended for all HIV patients, despite the fact that it is typically ineffective for treating KSHV infection. In HIV-positive individuals, ART should be given concurrently with KSHV-MCD-specific therapy. With the right KSHV medication, patients with HIV-associated KSHV may experience prolonged remissions on ART. ART lowers HIV-related mortality even though its effectiveness in preventing relapses has not been established [58]. However, rituximab, a humanized monoclonal antibody targeting the CD20 antigen on B-cells, was developed, and this led to a significant improvement in treatment responses and survival. Rituximab-based therapy have resulted in a dramatic improvement, with the majority of recent trials having a 5-year overall survival rate of more than 90%. Clinicians need to be on the lookout for KSHV relapse and the emergence of other KSHV-associated disorders as patients with KSHV-MCD continue to survive longer with proven and experimental treatment regimens [59].

HTLV-1

Human T-lymphotropic viruses (HTLV) are a family of human retroviruses recognized for causing oncogenic and other inflammatory and immunosuppressive diseases. HTLV-1 is the most clinically significant member of the family, having been demonstrated as a pathogen capable of inducing malignant disease and widely regarded as one of the strongest human oncogenic pathogen. The first human retrovirus discovered was HTLV-1, which was also one of the first viruses found to cause cancer in humans, alongside Epstein-Barr virus [60]. HTLV-1 can be transferred through breast feeding, sexual contact infected blood transfusions and needles. Approximately 5% of infected individuals develops (Adult T-cell Leukemia/Lymphoma) ATL after a clinical latency period of several decades [25].

Pathogenesis

HTLV-1 has standard retroviral genes, *gag*, *pol*, and *env*, as well as additional regulatory and accessory genes. Proviral DNA is produced through genomic viral RNA and incorporated into the host genome at random locations after infection. The viral gene products tax and hbz are associated with oncogenic transformation and are involved in the pathogenesis of ATL [61]. *Tax* starts the transformation process, whereas *hbz* sends signals to the cells needed for survival. However, *Tax* expression is frequently lost in ATL cases, while *hbz* is always expressed. The long latency and low incidence period of ATL suggest that both cellular genetic and epigenetic changes, in addition to HTLV-1 viral gene effects, are required for disease development. Several investigations have discovered a wide variety of biological genes and

pathways that are frequently altered or mutated in ATL cells [60, 61].

A rare form of non-T-cell Hodgkin's cancer called ATL is brought on by the HTLV-1 human retrovirus. Although though only a tiny percentage of HTLV-1 infected people acquire ATL, the clinical prognosis is poor for rapidly expanding subtypes. Recent advancements in treatment options have improved patient outcomes, but due to the heterogeneous nature of the disease, it is challenging to determine the best treatment for each individual patient. Research is required to find novel targets and create treatments to stop or halt the course of ATL [25].

Treatment

In particular, RNA reverse transcription, viral polyprotein cleavage, and DNA integration are the key possible targets for antivirals. Antiretroviral may therefore only be effective against productively infected cells, or the infectious propagate, and not against non-producing infected cells. Antiretroviral are anticipated to have minimal efficacy, unless viral replication is initiated, in HTLV-1-infected patients because there is typically very little (if any) productive infection found in these patients. This could readily explain why antiretroviral are less effective in treating HTLV-1 infection than HIV infection. Consequently, considering that the possibility of treating HTLV-1 infected people with antiretroviral medication is yet debatable [62].

No vaccine exists to treat or prevent HTLV-1 infections. The notion of creating an HTLV-1 vaccine originally emerged in the early 1980s, and at first it appeared to be simpler than creating an HIV-1 vaccine. The HTLV-1 envelope gene, when expressed by a vaccinia vector, causes a partial protection against HTLV-1 infection in rodents, likely by the production of neutralizing antibodies targeted at the viral envelope, which is the basis for an effective active immunotherapy [63]. This discovery is supported by the finding that neonates of HTLV-1-infected mothers are protected against HTLV-1 infection for as long as breastfeeding permits the transfer of maternal antibodies, suggesting that neutralizing antibodies may help to prevent HTLV-1 transmission. Despite this intriguing advantage, HTLV-1 cell-to-cell transfer and the clonal proliferation of infected cells without the production of viral proteins may both work to reduce the amount of HTLV-1 envelope exposed in vivo. Finally, it is hoped that the development of novel antiretroviral or vaccine with targets unique to HTLV-1 and/or the initiation of early antiretroviral therapies may alter perceptions of diseases brought on by HTLV-1 [64].

Merkel Cell Polyomavirus

The Merkel cell polyomavirus (MCPyV) has a genome similar to other human polyomaviruses, which is a circular, double-stranded DNA genome of 5,387 base-pairs in length. It is a member of the *Orthopolyomavirus* genus and the *Polyomaviridae* family. It was first discovered in 2008 [66]. In humans, it causes Merkel cell carcinoma (MCC) which is a rare uncommon, highly aggressive cancer. The idea that MCC may have a pathogenic origin was initially suggested due to the observation that the incidence of MCC was significantly higher, by over ten times, in individuals with HIV-1 AIDS relative to the general public [26]. A general model of tumor development can be proposed for MCPyV. The virus is acquired in adulthood, and while the mode of transmission is still unknown, it is believed to occur through the skin as the virus is part of the skin's microflora. Immunosuppression caused by aging, HIV-AIDS, medications, or UV exposure resuls to a decline in immunosurveillance, resulting in MCPyV reactivation and the potential for mutations associated with tumorigenesis. UV radiation and other external stimuli may increase the probability of mutations. In cells that have integrated a replication-defective form of MCPyV, the expression of Viral oncogenes cause clonal growth and the progression of cancer, and eventually, the development of MCC, regardless of the sequence of mutations [67].

The early viral gene region (EVGR) encodes for ST (small T antigen), and LT, 57kT (a spliced form of LT). An alternative open reading frame from LT contains the ALTO. The late viral gene region (LVGR) encodes VP1 and VP2 which are viral coat proteins and also encodes a microRNA regulating antigen T levels. The 72 VP1 pentamers that make up the polyomavirus virion are each coated on the inner surface by a VP2 molecule. According to the VP1 serology assay, MCPyV infection can start as early as a few months of age and become more common as people age, with 70–90% of adults showing signs of chronic infection [68].

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Pathogenesis

T antigen is mainly responsible for the carcinoma. The Large T antigen (LT) of merkel cell polyomavirus (MCPyV) is a protein of 817 residues, but an alternative form, 57kT, has a central region deletion and retains only the 100 residues on C-terminal. Although its purpose is uncertain, 57kT exhibits growth-suppressing properties. Retinoblastoma tumour suppressor protein RB is bound by MCPyV LT to inactivate it and trigger cell cycle-regulated genes. This binding is caused by the LXCXE motif, which is necessary for transforming action [69]. The proliferation of MCCP tumours depends on the adsorption and inactivation of RB. MCPyV LT activates p53 through its association with RB or USP7, which is a deubiquitinase enzyme that regulates MDM2 levels and p53. LT also binds to VPS39, but the significance of this activity is not known. Due to viral genome alterations, LT is expressed in a shortened form in all MCC cancers and the truncated forms are expressed in the nucleus and cytoplasm [76]. These truncations result in the loss of the nuclear localization sequence, origin binding and helicase domains, growth-suppressing activities, and possible viral antigens that could stimulate the immune system to fight cancer leading to a rare form of highly aggressive malignancy known as Merkel cell carcinoma [26, 68].

The identification of MCPyV and its potential involvement in MCC underscores the ongoing importance of polyomavirus and DNA tumor virus research. The current resurgence of interest in these fields, along with advancements in technology, has led to the discovery of additional human viruses and thus it will continue in future [67].

Treatment

Merkel cell cancer caused by MCPyV should be treated by following the same Cancer Network recommendations. Nevertheless, because the results may have an impact on follow-up, quantification of MCPyV oncoprotein antibodies may be taken into consideration during the first workup. Seronegative patients may be at increased risk for recurrence, while growing titers in seropositive patients may be an early sign of recurrence [70]. Wide local excision along with sentinel lymph node biopsy is the basis of the therapy of nonmetastatic MCC. For sentinel lymph node biopsy results, metastatic disease, or clinically positive nodes, baseline imaging is advised. For nodal disease that has been clinically identified as well as pathology-proven, lymphadenectomy or nodal radiotherapy is needed. When no nodal illness has been verified, nodal radiotherapy may be explored for high-risk patients [71].

Extensive local excision may not always be necessary, and a recent evaluation found that in cases of early-stage MCC without nodal disease, Mohs micrographic surgery had long-term survival and increased cancer clearing rates. Another recent analysis found that local and regional radiation monotherapy would be a viable option for treating stage I, II, or III illness that is incurable. The US Food and Drug Administration only granted approval Avelumab, a completely human anti-PD-L1 monoclonal antibody, as a treatment for MCC. In a phase II clinical trial, Avelumab showed a therapeutic response in 33% of patients, with a median general survival of 11 months. Anti-PD-L1 antibodies nivolumab and pembrolizumab are also being investigated for treatment in metastatic MCC [72].

Epstein Bar Virus

The very first virus connected to human cancer was the Epstein-Barr virus, following its detection in the tumor cells of pediatric Burkitt lymphoma patients [7]. The Herpes family double-stranded DNA virus Epstein-Barr virus (EBV) has been linked to a number of malignancies is associated with various cancers, including gastric carcinoma (GC), Hodgkin's lymphoma (HL), nasopharyngeal carcinoma (NPC) and Burkitt's lymphoma (BL). Although extensive research has been conducted, the etiology of EBV-related cancers is not fully comprehended. It is probable that other factors, such as genetic mutations, environmental circumstances, and underlying diseases, considering that only a small portion of people with EBV infection go on to develop cancer [13, 27].

Pathogenesis

EBV has been categorized as a group 1 carcinogen, which is a category only for compounds that are known to cause cancer in people [16]. One of the hallmarks of EBV infection is its potential to immortalize normal B cells *in vitro* conditions, which means it can prevent

these cells from undergoing programmed cell death, allowing them to survive and proliferate indefinitely. This characteristic is regarded to be crucial to EBV's capacity to induce malignancy, as it allows infected cells to accumulate mutations and genomic instability over time, leading to the development of malignant tumors [17].

EBV can mediate infection via two mechanisms: latent infection and lytic infection. When a virus is latently infected, it does not manifest any symptoms. However occasionally, the virus can enter a lytic state, in which it releases fresh viral particles and induces the growth of cancerous tumors from cells [77]. The molecular events involved in this process, such as the expression of viral proteins that prevent apoptosis, promote genomic instability, and cause unchecked proliferation and migration of cells are well understood and are known to signal the beginning of a tumor followed by persistent tumor maintenance, although the true etiology is not fully understood yet but the involvement of human leukocyte antigens (HLA] [27]. In addition to its ability to induce oncogenesis, EBV also employs a variety of mechanisms to evade the host immune response, which allows the virus to persist and continue to cause cancer. For instance, the virus only expresses a tiny subset of its genes during the initial lytic infection, helping to thwart the host's immune system from recognizing it [78]. EBV can imitate the properties of IL-10, a cytokine that aids in the suppression of the immune response, and it controls the production of several cytokines that are important for the host immune response, including as TNF-, IL-1, and IL-6 [79]. Finally, it is worth noting that the malignant pathogenesis of EBV is enhanced by a number of factors, includes a chronically inflamed host microenvironment and a weakened host immune system brought on by specific medical disorders. These elements may encourage the development of cancer by encouraging the proliferation and spread of EBV-infected cells [80].

Treatment

Viral latency proteins are expressed in EBV-associated cancers and are used in therapeutic EBV vaccines that were created to treat people who have EBV lymphomas or nasopharyngeal carcinoma. These vaccines contain replication-defective vectors, such as recombinant vaccinia Ankara that expresses LMP2 and EBNA1 fragments, dendritic cells from people infected with modified adenovirus that encodes LMP2 [73]. EBV vaccines, however, have the potential to cause a “unusual” or “excessive” immune response against EBV, which could result in the onset or aggravation of autoimmune illnesses like Multiple Sclerosis (MS). In contrast, a transitory sterilizing immunity induced by an EBV vaccination can theoretically postpone the start of a primary infection and cause MS to become more severe later in life [74].

EBV has been linked to MS through a process known as molecular mimicry wherein antibodies or T cells to EBV proteins interact with CNS proteins. If this theory is accurate, immunization with certain EBV protein fragments, such as EBNA1, that interact with CNS proteins can trigger an immune response that raises the risk of MS. Consequently, it is important to carefully assess which viral antigens would be contained in EBV vaccinations [75].

Human Papillomavirus

The human papillomavirus (HPV) is a sexually transmitted infection that is common throughout the world and is strongly associated with cervical cancer. Most individuals who engage in multiple sexual activities will contract HPV at some point in their lives [17]. The *Papillomaviridae* family contains the double-stranded DNA virus known as HPV, which is divided into two categories: low-risk HPVs (LR-HPVs), which cause anogenital and cutaneous warts, and high-risk HPVs (HR-HPVs), which lead to anogenital and oropharyngeal cancers, such as anal, cervical, vaginal, penile and vulvar cancers. Cervical cancer is the third most common malignancy in women among these [81]. More than 130 HPV types are classified as high or low risk depending on their ability to cause cancer through persistent infection. The primary cause of cancer is high-risk HPV types types (18, 39, 35, 31, 35, 16, 51, 56, 58, 52, 66, 59, and 33). Types 16 and 18 of this group of high-risk HPV are in charge of 70% of cervical cancer cases globally. Low-risk HPV types such as 11, 42, 44, 6, 43, 53, 44, 61, 54, 81, and 72 are not that prominent and have a lower potential to cause cancer [17, 18].

Pathogenesis

Most HPV infections are quickly eliminated by the immune system, and viral DNA incorporation into the host cell is rare. Although rapid tumor cell transformation caused by viral DNA incorporation is possible, cancer cannot be caused by viral DNA incorporation alone without other genetic and epigenetic changes. The E6 and E7 oncoproteins are the main drivers of HPV-associated cancer, as they modify the cell cycle and apoptosis, and their dysregulated expression is caused by disruption of the E2 protein's transcriptional repression [82]. The E5 oncogene, which affects immunological functions like antigen presentation and inflammation, is expressed by HPV and can lead to immune evasion. The immune response is a crucial defense against HPV infection and cervical carcinogenesis [83].

The HPV oncoproteins E6 and E7 play a significant role in neoplastic transformation by altering the cell cycle, regulating apoptosis, and disrupting key tumor suppressor proteins [84]. E7 inactivates pRb, leading to uncontrolled cellular proliferation, while E6 promotes the proteosomal degradation of the tumor suppressor p53 through its interaction with E6AP [82, 85]. The HPV-induced degradation of p53 is a crucial aspect of neoplastic transformation, and its concentration is often lower in HPV-infected cells than in healthy cells. E6AP is an E3 ubiquitin protein ligase that regulates the binding of E6 to p53. E6AP turnover is increased in the presence of E6, which enhances its enzymatic activity in the cellular environment [82].

Treatment

The vaccines are ineffective if an individual already has an HPV infection or cervical lesions caused by HPV. HPV vaccines such as Gardasil and Cervarix prevent infection by stimulating the production of neutralizing antibodies against specific types of HPV. They are primarily used to prevent cervical cancer and are most effective when administered before exposure to the virus. The recommended age for vaccination is between 11–12 years old, with the possibility of receiving the vaccine up to age 26. The vaccines are given in three shots over a six-month period [28].

Investigations are being done on therapeutic vaccinations and preventative vaccines based on L2. L2-based vaccines have the potential to provide protection against a wide variety of HPV strains since L2 sequences are substantially conserved across HPV types. Additionally, numerous immunotherapies and specific therapies for HPV-related cancers are being researched, and several have US Food and Drug Administration approval [72].

Conclusion and Future Perspective

This review aims to provide a comprehensive exploration of viral oncogenesis, contributing to a broader understanding of oncoviruses and their pathogenesis. The oncogenic virus infections cause up to 20% of human cancers presents an opportunity for further research to address knowledge gaps. Removing the causative agent not only controls the infectious disease but also prevents associated cancers. The presence of viruses in the body and underlying diseases are major causes of cancer. Vaccination programs, such as for HBV and HPV, have demonstrated that cancer prevention can limit the oncogenic effects of viruses, but currently there are limited oncovirus vaccines available. The COVID-19 pandemic has provided us with opportunities to use advanced research facilities to develop not only vaccines but also detection markers for cancer prevention. The majority of microbe-related markers can help with secondary and tertiary prevention of malignancies linked to infections. To find new cancers and vaccines linked to infections, however, further study is necessary. The majority of the current understanding regarding the connection between microorganisms and cancer is concentrated in Western nations. This article advocates for the need to expand our understanding of these mechanisms and develop effective prevention strategies in developing countries to protect their populations from these infections.

This review digs into the complex realm of oncogenic viruses and pathogenesis, revealing fresh insight on their captivating modes of action and key role in cancer formation. However, investigating viral-induced tumors might potentially help answer crucial questions in cancer biology. These could include determining cancer's evolutionary bottlenecks, locating the most vulnerable regions in the regulation of genes networks for virus induced cancer, and establishing methods to reduce genetic and environmental variables that contribute to oncogenesis. Researchers may also investigate tech-

niques to reverse tissue microenvironment factors that favor cancer cell evolution. Ultimately, getting a full grasp of the factors behind viral infections and cancer growth might provide a better ordered scientific structure for study and open up new treatment approaches.

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Conflicts of Interest

The authors have no financial conflicts of interest to declare.

References

1. Krump NA, You J. 2018. Molecular mechanisms of viral oncogenesis in humans. *Nat. Rev. Microbiol.* **16**: 684-698.
2. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. 2020. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob. Health* **8**: e180-e190.
3. Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. 2015. Global burden of gastric cancer attributable to *Helicobacter pylori*. *Int. J. Cancer* **136**: 487-490.
4. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al.* 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J. Pathol.* **189**: 12-19.
5. Cancer statistics CDC. Available online: https://www.cdc.gov/cancer/hpv/statistics/cases.htm. Accessed Jan 24, 2023.
6. Fugl A, Andersen CL. 2019. Epstein-Barr virus and its association with disease - a review of relevance to general practice. *BMC Fam. Pract.* **20**: 62.
7. Epstein MA, Achong BG, Barr YM. 1964. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* **1**: 702-703.
8. Zur Hausen H, de Villiers EM. 2014. Cancer "Causation" by infections-individual contributions and synergistic networks. *Semin. Oncol.* **41**: 860-875.
9. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, *et al.* 2009. Decreased incidence of hepatocellular carcinoma in Hepatitis B vaccinees: A 20-year follow-up study. *J. Natl. Cancer Inst.* **101**: 1348-1355.
10. Lu T, Seto WK, Zhu RX, Lai CL, Yuen MF. 2013. Prevention of hepatocellular carcinoma in chronic viral hepatitis B and C infection. *World J. Gastroenterol.* **19**: 8887-8894.
11. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, *et al.* 2012. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ* **344**: e1401.
12. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. 2013. Human papillomavirus and cervical cancer. *Lancet* **382**: 889-899.
13. Chang MH. 2011. Hepatitis B virus and cancer prevention. *Recent Results Cancer Res.* **188**: 75-84.
14. Yasunaga JI, Matsuoka M. 2018. Oncogenic spiral by infectious pathogens: Cooperation of multiple factors in cancer development. *Cancer Sci.* **109**: 24-32.
15. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. 2016. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob. Health* **4**: e609-e616.
16. *Biological agents*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100B. pp. 1-475. (Accessed Jan. 26, 2023).
17. Ahmed HG, Bensumaidea SH, Alshammari FD, Alenazi FSH, ALmutlaq BA, Alturkstani MZ, *et al.* 2017. Prevalence of human papillomavirus subtypes 16 and 18 among Yemeni patients with cervical cancer. *Asian Pac. J. Cancer Prev.***18**: 1543-1548.
18. Steben M, Duarte-Franco E. 2007. Human papillomavirus infection: epidemiology and pathophysiology. *Gynecol. Oncol.* **107**: S2-S5.
19. Teufel A, Staib F, Kanzler S, Weinmann A, Schulze-Bergkamen H, Galle PR. 2007. Genetics of hepatocellular carcinoma. *World J. Gastroenterol.* **13**: 2271-2282.
20. Hamdane N, Jühling F, Crouchet E, el Saghire H, Thumann C, Oudot MA, *et al.* 2019. HCV-induced epigenetic changes associated with liver cancer risk persist after sustained virologic response. *Gastroenterology* **156**: 2313-2329.e7.
21. Lin MV, King LY, Chung RT. 2015. Hepatitis C virus-associated cancer. *Ann. Rev. Pathol.* **10**: 345-370.
22. Goncalves PH, Ziegelbauer J, Uldrick TS, Yarchoan R. 2017. Kaposi sarcoma herpesvirus-associated cancers and related diseases. *Curr. Opin. HIV AIDS* **12**: 47-56.
23. Guasparri I, Keller SA, Cesarman E. 2004. KSHV vFLIP is essential for the survival of infected lymphoma cells. *J. Exp. Med.* **199**: 993-1003.
24. Casper C, Corey L, Cohen JI, Damania B, Gershon AA, Kaslow DC, *et al.* 2022. KSHV (HHV8) vaccine: promises and potential pitfalls for a new anti-cancer vaccine. *NPJ Vaccines* **7**: 108.
25. Panfil AR, Martinez MP, Ratner L, Green PL. 2016. Human T-cell leukemia virus-associated malignancy. *Curr. Opin. Virol.* **20**: 40-46.
26. DeCaprio JA. 2017. Merkel cell polyomavirus and Merkel cell carcinoma. Philos. *Trans. R Soc. Lond. B Biol. Sci.* **372**: 20160276.
27. Bakkalci D, Jia Y, Winter JR, Lewis JE, Taylor GS, Stagg HR. 2020. Risk factors for Epstein Barr virus-associated cancers: a systematic review, critical appraisal, and mapping of the epidemiological evidence. *J. Glob. Health* **10**: 010405.
28. Bansal A, Singh MP, Rai B. 2016. Human papillomavirus-associated cancers: A growing global problem. *Int. J. Appl. Basic Med. Res.* **6**: 84-89.
29. Wiest T, Schwarz E, Enders C, Flechtenmacher C, Bosch FX. 2002. Involvement of intact HPV16 E6/E7 gene expression in head and neck cancers with unaltered p53 status and perturbed pRb cell cycle control. *Oncogene* **21**: 1510-1517.
30. Ganem D, Schneider RJ. 2001. Hepadnaviridae and their replication. In: Knipe DM, Howley PM, Griffin DE, Martin MA, Lamb RA,

Roizman B, *et al*. 2020. Viral Hepatitis B and C Detection among Ebola Survivors and Health Care Workers in Makeni, Sierra Leone. Fields Virology. 4.
31. Liang TJ. 2009. Hepatitis B: the virus and disease. *Hepatology* **49**: S13-S21.
32. Gavilanes F, Gonzalez-Ros JM, Peterson DL. 1982. Structure of hepatitis B surface antigen. Characterization of the lipid components and their association with the viral proteins. *J. Biol. Chem.* **257**: 7770-7777.
33. Gerlich WH, Robinson WS. 1980. Hepatitis B virus contains protein attached to the 5' terminus of its complete DNA strand. *Cell* **21**: 801-809.
34. Hruska JF, Clayton DA, Rubenstein JL, Robinson WS. 1977. Structure of hepatitis B Dane particle DNA before and after the Dane particle DNA polymerase reaction. *J. Virol*. **21**: 666-672.
35. Liaw Y-F, Chu C-M. 2009. Hepatitis B virus infection. *Lancet* **373**: 582-592.
36. Nelson NP, Easterbrook PJ, McMahon BJ. 2016. Epidemiology of Hepatitis B virus infection and impact of vaccination on disease. *Clin. Liver Dis.* **20**: 607-628.
37. Lim JK, Nguyen MH, Kim WR, Gish R, Perumalswami P, Jacobson IM. 2020. Prevalence of chronic Hepatitis B virus infection in the United States. *Am. J. Gastroenterol.* **115**: 1492-1438.
38. Peng CY, Chien RN, Liaw YF. 2012. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. *J. Hepatol*. **57**: 442-450.
39. Arbuthnot P, Kew M. 2001. Hepatitis B virus and hepatocellular carcinoma. *Int. J. Exper. Pathol.* **82**: 77-100.
40. El-Serag HB, Rudolph KL. 2007. Hepatocellular carcinoma: Epidemiology and molecular carcinogenesis. *Gastroenterology* **132**: 2557-2576.
41. Levrero M, Zucman-Rossi J. 2016. Mechanisms of HBV-induced hepatocellular carcinoma. *J. Hepatol*. **64**: S84-S101.
42. Venook AP, Papandreou C, Furuse J, de Guevara LL. 2010. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* **15**: 5-13.
43. Pietschmann T, Brown RJP. 2019. Hepatitis C Virus. *Trends Microbiol.* **27**: 379-380.
44. Tibbs CJ. 1995. Methods of transmission of hepatitis C. *J. Viral Hepat*. **2**: 113-119.
45. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hürter D, *et al.* 1998. Prognosis of chronic hepatitis c: Results of a large, prospective cohort study. *Hepatology* **28**: 1687-1695.
46. Khullar V, Firpi RJ. 2015. Hepatitis C cirrhosis: New perspectives for diagnosis and treatment. *World J. Hepatol*. **7**: 1843-1855.
47. Rehermann B, Nascimbeni M. 2005. Immunology of hepatitis B virus and hepatitis C virus infection. *Nat. Rev. Immunol*. **5**: 215-229.
48. Hanahan D, Weinberg RA. 2011. Hallmarks of cancer: The next generation. *Cell* **144**: 646-674.
49. Arzumanyan A, Reis HMGPv, Feitelson MA. 2013. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat. Rev. Cancer* **13**: 123-135.
50. Levrero M, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M. 2009. Control of cccDNA function in hepatitis B virus infection. *J. Hepatol*. **51**: 581-592.
51. Hoshida Y, Fuchs BC, Bardeesy N, Baumert TF, Chung RT. 2014. Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma. *J. Hepatol*. **61**: S79-S90.
52. Yarchoan R, Uldrick TS. 2018. HIV-associated cancers and related diseases. *New Eng. J. Med*. **378**: 1029-1041.
53. Repáraz D, Aparicio B, Llopiz D, Hervás-Stubbs S, Sarobe P. 2022. Therapeutic vaccines against hepatocellular carcinoma in the immune checkpoint inhibitor era: Time for neoantigens? *Int. J. Mol. Sci*. **23**: 2022.
54. Mesri EA, Cesarman E, Boshoff C. 2010. Kaposi's sarcoma and its associated herpesvirus. *Nat. Rev. Cancer* **10**: 707-719.
55. Chakraborty S, Valiya Veettil M, Chandran B. 2012. Kaposi's Sarcoma associated herpesvirus entry into target cells. *Front. Microbiol*. **3**: 6.
56. Sharma-Walia N, Paul AG, Bottero V, Sadagopan S, Veettil MV, Kerur N, *et al.* 2010. Kaposi's Sarcoma associated Herpes virus (KSHV) induced COX-2: A key factor in latency, inflammation, angiogenesis, cell survival and invasion. *PLoS Pathog.* **6**: e1000777.
57. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, *et al.* 2013. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* **8**: e81355.
58. Oksenhendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranel J, *et al.* 1996. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* **10**: 61-67.
59. Lurain K, Yarchoan R, Uldrick TS. 2018. Treatment of Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Hematol. Oncol. Clin*. **32**: 75-88.
60. Tagaya Y, Matsuoka M, Gallo R. 2019. 40 years of the human T-cell leukemia virus: past, present, and future. *F1000Res*. **8**: F1000.
61. Matsuoka M, Jeang K-T. 2007. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. *Nat. Rev. Cancer* **7**: 270-280.
62. Marino-Merlo F, Balestrieri E, Matteucci C, Mastino A, Grelli S, Macchi B. 2020. Antiretroviral therapy in HTLV-1 infection: an updated overview. *Pathogens* **9**: 342.
63. Bangham CR, Miura M, Kulkarni A, Matsuoka M. 2019. Regulation of latency in the human T cell leukemia virus, HTLV-1. *Ann. Rev. Virol.* **6**: 365-385.
64. Tu JJ, Maksimova V, Ratner L, Panfil AR. 2022. The past, present, and future of a human T-cell leukemia virus type 1 vaccine. *Front. Microbiol.* **13**: 897346.
65. Arnold J, Zimmerman B, Li M, Lairmore MD, Green PL. 2008. Human T-cell leukemia virus type-1 antisense-encoded gene, Hbz, promotes T-lymphocyte proliferation. *Blood* **112**: 3788-3797.
66. Spurgeon ME, Lambert PF. 2013. Merkel cell polyomavirus: A newly discovered human virus with oncogenic potential. *Virology* **435**: 118-130.
67. Stakaitytė G, Wood J, Knight LM, Abdul-Sada H, Adzahar NS,

Nwogu N, *et al.* 2014. Merkel cell polyomavirus: Molecular insights into the most recently discovered human tumour virus. *Cancers* **6**: 1267-1297.
68. DeCaprio JA. 2021. Molecular pathogenesis of Merkel cell carcinoma. *Ann. Rev. Pathol.* **16**: 69-91.
69. Hesbacher S, Pfitzer L, Wiedorfer K, Angermeyer S, Borst A, Faferkamp S, *et al*. 2016. RB1 is the crucial target of the Merkel cell polyomavirus large T antigen in Merkel cell carcinoma cells. *Oncotarget* **7**: 32956-32968.
70. Patel P, Modi C, McLellan B, Ohri N. 2018. Radiotherapy for inoperable Merkel cell carcinoma: a systematic review and pooled analysis. *Dermatol. Pract. Concept.* **8**: 149.
71. Walocko FM, Scheier BY, Harms PW, Fecher LA, Lao CD. 2016. Metastatic Merkel cell carcinoma response to nivolumab. *J. Immunother. Cancer* **4***:* 79.
72. Haley CT, Mui UN, Vangipuram R, Rady PL, Tyring SK. 2019. Human oncoviruses: Mucocutaneous manifestations, pathogenesis, therapeutics, and prevention: papillomaviruses and Merkel cell polyomavirus. *J. Am. Acad. Dermatol.* **81***:* 1-21.
73. Bjornevik K, Münz C, Cohen JI, Ascherio A. 2023. Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications. *Nat. Rev. Neurol.* **19**: 160-171.
74. Zeng Y, Si YF, Lan GP, Wang Z, Zhou L, Tang MZ, *et al.* 2020. LMP2-DC vaccine elicits specific EBV-LMP2 response to effectively improve immunotherapy in patients with nasopharyngeal cancer. *Biomed. Environ. Sci.* **33***:* 849-856.
75. Nickles E, Dharmadhikari B, Yating L, Walsh RJ, Koh LP, Poon M, *et al*. 2022. Dendritic cell therapy with CD137L-DC-EBV-VAX in locally recurrent or metastatic nasopharyngeal carcinoma is safe and confers clinical benefit. *Cancer Immunol. Immunother.* **71**: 1531-1543.
76. Wang X, Li J, Schowalter RM, Jiao J, Buck CB, You J. 2012. Bromodomain protein Brd4 plays a key role in Merkel cell polyomavirus DNA replication. *PLoS Pathog.* **8**: e1003021.
77. Prabhu SR, Wilson DF. 2016. Evidence of epstein-barr virus association with head and neck cancers: a review. *J. Can. Assoc.* **82**: g2.
78. Tempera I, Lieberman PM. 2014. Epigenetic regulation of EBV persistence and oncogenesis. *Semin. Cancer Biol.* **26**: 22-29.
79. Fox RI, Luppi M, Pisa P, Kang HI. 1992. Potential role of Epstein-Barr virus in Sjögren's syndrome and rheumatoid arthritis. *J. Rheumatol. Suppl.* **32**: 18-24.
80. Rickinson AB. 2014. Co-infections, inflammation and oncogenesis: Future directions for EBV research. *Semin. Cancer Biol.* **26**: 99-115.
81. Kombe Kombe AJ, Li B, Zahid A, Mengist HM, Bounda G-A, Zhou Y, *et al*. 2021. Epidemiology and burden of human papillomavirus and related diseases, molecular pathogenesis, and vaccine evaluation. *Front. Public Health* **8**: 552028.
82. Narisawa-Saito M, Kiyono T. 2007. Basic mechanisms of high-risk human papillomavirus-induced carcinogenesis: Roles of E6 and E7 proteins. *Cancer Sci.* **98**: 1505-1511.
83. de Freitas AC, de Oliveira THA, Barros MR, Venuti A. 2017. hrHPV E5 oncoprotein: immune evasion and related immunotherapies. *J. Exper. Clin. Cancer Res.* **36**: 71.
84. Wang X, Huang X, Zhang Y. 2018. Involvement of human papillomaviruses in cervical cancer. *Front. Microbiol.* **9**: 2896.
85. Howley PM. 2006. Warts, cancer and ubiquitylation: lessons from the papillomaviruses. *Trans. Am. Clin. Climatol. Assoc.* **117**: 113-127.