Viruses and Carcinogenesis

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Abstract

Oncoviruses play a role in approximately 15% or more of all human cancers. A significant portion of the global population carries at least one of these oncoviruses, yet only a small percentage of these individuals progress to the development of cancer. The intricate interplay between host and viral factors constitutes a complex process that collaborates in the establishment of a microenvironment conducive to oncogenesis. Currently, there are eight recognized human oncoviruses, namely Epstein-Barr Virus (EBV), Human Papillomavirus (HPV), Hepatitis B and C viruses (HBV and HCV), Human T-cell lymphotropic virus-1 (HTLV-1) and Human T-cell lymphotropic virus-2 (HTLV-2), Human Herpesvirus-8 (HHV-8), and Merkel Cell Polyomavirus (MCPyV). These viruses have been shown to be a major causative agent in one or more human cancers in which viral nucleic acids have been detected. The mechanism of oncogenesis has also been explored, which demonstrated differing or similar strategies utilized by the viruses on infection of host cells to bypass cell cycle check point regulators leading to cell proliferation and a tumorigenic phenotype.

Introduction

Carcinogenesis involves hereditary, cytological, and cellular transformations that lead to the development of malignant cancers (Brucher and Jamall, 2014). There are ten characteristics or abilities of any agent that determines it as a carcinogen which includes 1) act as an electrophile either directly or after metabolic activation; 2) be genotoxic; 3) alter DNA repair or cause genomic instability; 4) induce epigenetic alterations; 5) induce oxidative stress; 6) induce chronic inflammation; 7) be immunosuppressive; 8) modulate receptor-mediated effects; 9) cause immortalization; and 10) alter cell proliferation, cell death, or nutrient supply (Smith *et al.*, 2016). Oncogenic viruses encompass both DNA and RNA viruses and are recognized as significant agents responsible for causing diseases in humans and animals. Epidemiological and molecular studies have subsequently confirmed the association between oncogenic viruses and different type of cancer, and the oncogenic viruses are carcinogenic infectious agents in humans listed by the International Agency for Research on Cancer (IARC) (World Health Organization). Different viral antigens induces reactive oxygen species and acts indirectly as electrophiles (Schwarz, 1996). Viruses do induce DNA breaks that allows them to incorporate in the host genome. These DNA breaks leads to chromosomal translocations and thus viruses act like genotoxic agents and induces genomic damage and instability (Lavia *et al.*, 2003; Ryan *et al.*, 2016). It's important to note that oncoviruses alone are not sufficient for tumor formation; other factors, such as chronic inflammation, environmental mutagens, and immunosuppression, also play a role in cancer development, resulting in a relatively low incidence of viral-induced carcinogenesis (Chowdhary *et al.*, 2023). Inflammation plays a crucial role in the progression of tumors (Singh *et al.*, 2019). It is a beneficial response initiated by damaged tissue releasing cellular factors. In response to these signals, white blood cells are activated and release cytokines that instruct local cells to proliferate and repair the damaged tissue (Chen *et al.*, 2018). Once the tissue is restored, the inflammatory process ceases. However, in cases of chronic inflammation, the process persists even in the absence of injury or when the injury has healed. Prolonged inflammation can also lead to DNA damage and the development of cancer (Chen *et al.*, 2018). The causes of chronic inflammation can be diverse, including infectious agents like viruses, bacteria, or parasites, as well as non-infectious irritants, whether physical or chemical in nature (Zhao *et al.*, 2021b).

Recent findings have indicated that the use of nonsteroidal anti-inflammatory drugs may reduce the risk of cancer development (Kolawole and Kashfi, 2022). Environmental mutagens primarily encompass air pollutants, soil and water contamination, and contamination of food. Exposure to environmental mutagens does not guarantee that an individual will develop cancer; rather, it depends on the duration and level of exposure as well as the individual's genetic background. Understanding these factors, along with the sources and extent of exposure, can help in preventing cancer development (Anand *et al.*, 2008). It is now widely recognized that failure of the immune system contributes to the success of cancer development (Finn, 2012). Recent research has demonstrated the infiltration of tumors by Treg cells plays a critical role in tumor tolerance (Tanchot *et al.*, 2013). Consequently, targeting Treg cells and reducing the tumor's immunosuppressive environment, while also activating the innate anti-tumor environment, are considered promising advances in cancer treatment (Dwarakanath *et al.*, 2018).

Cancers are not contagious in the conventional sense, meaning they are not transmitted from patients to their close contacts. However, global studies have revealed that approximately one in six cancers worldwide has an infectious origin (Thun *et al.*, 2010). It's important to note that this estimated fraction is likely a significant underestimate, particularly in developing countries with limited or non-existent cancer registries. In some regions of Africa, such as Kampala in Uganda, which have robust reporting systems, it has been shown that up to 50% of newly diagnosed cancers are attributed to infectious agents (Parkin *et al.*, 2020). Notably, these infections tend to affect a younger population than what is traditionally observed in North American or European settings. Some

cancer registries may exclude non-melanoma skin cancers or attribute deaths to HIV rather than HIV-related cancers. Additionally, these estimates often do not account for newly discovered infectious causes of cancer, such as the Merkel cell polyomavirus, or new associations between known viruses and specific tumors. For instance, the Epstein–Barr virus (EBV) is found to cause more cases of gastric carcinoma than lymphoma (Hirabayashi *et al.*, 2023). Various infectious agents, including bacteria (such as Helicobacter pylori in stomach cancer and mucosal-associated lymphomas) and helminths (linked to carcinomas of the urinary bladder and gall bladder), are associated with malignancy (Hirabayashi *et al.*, 2023). However, out of the two million new cancer cases that arise from infections each year, approximately 1.6 million are a consequence of persistent infection by oncogenic viruses (Chang *et al.*, 2017). This chapter delves into the latest developments concerning these viruses and their mechanisms of action.

The idea that a transmissible agent might contribute to certain types of human cancer traces back to observations made by the physician Domenico Rigoni-Stern in 1842 (Chang *et al.*, 2017). When analyzing death certificates for women in Verona from 1760 to 1839, he noticed that while nuns had an increased risk of breast cancer, they had a lower risk of cervical cancer compared to married women and notably lower than sex workers (Scotto and Bailar, 1969). He deduced that sexual contact played a role in the development of cervical cancer (Scotto and Bailar, 1969). Although during Rigoni-Stern's time there was no knowledge of hormones or viruses, it is interesting to note that 120 years later, in 1966, the Nobel Prize for Physiology and Medicine was awarded both to Charles Huggins, "For his discoveries concerning hormonal treatment of cancer," and to Peyton Rous, "For his discovery of tumor-inducing viruses"(Chang *et al.*, 2017). The isolation of Rous's eponymous sarcoma virus in chickens occurred 55 years prior to this recognition, marking the longest "incubation period" between discovery and Nobel Prize acknowledgment. It took an additional 42 years before Harald zur Hausen received a similar honor for discovering strains of human papillomavirus (HPV) responsible for cervical cancer (Mathew *et al.*, 2009). Tumor viruses played a pioneering role in the early days of molecular cell biology, with Nobel awards going to Renato Dulbecco, Howard M Temin, and David Baltimore in 1975 for in vitro cell transformation by viruses and for reverse transcriptase (Chang *et al.*, 2017); to Baruch S Blumberg in 1976 for elucidating hepatitis B virus; to J Michael Bishop and Harold E Varmus in 1989 for uncovering the cellular origin of retroviral oncogenes; and to Richard Roberts and Philip Sharp in 1993 for the discovery of RNA splicing in adenovirus (Suran, 2020).

Viral oncogenes play a pivotal role in driving uncontrolled proliferation of host cells and produce novel viral gene-related proteins, ultimately leading to cellular transformation. Proto-oncogenes are the cellular counterparts of viral oncogenes, which can be transformed into an oncogenic state through mutations, amplifications, deletions, or chromosomal translocations induced by viral oncogenes (Cooper and Adams, 2022).

Oncogenes engage in a continuous struggle with tumor suppressor genes, which are responsible for safeguarding DNA and regulating cellular functions. However, in the context of cancer development, tumor suppressor genes may lose this battle, or viral oncogenes may prevail by causing the inactivation of these tumor suppressor genes (**Fig. 1**). Consequently, it

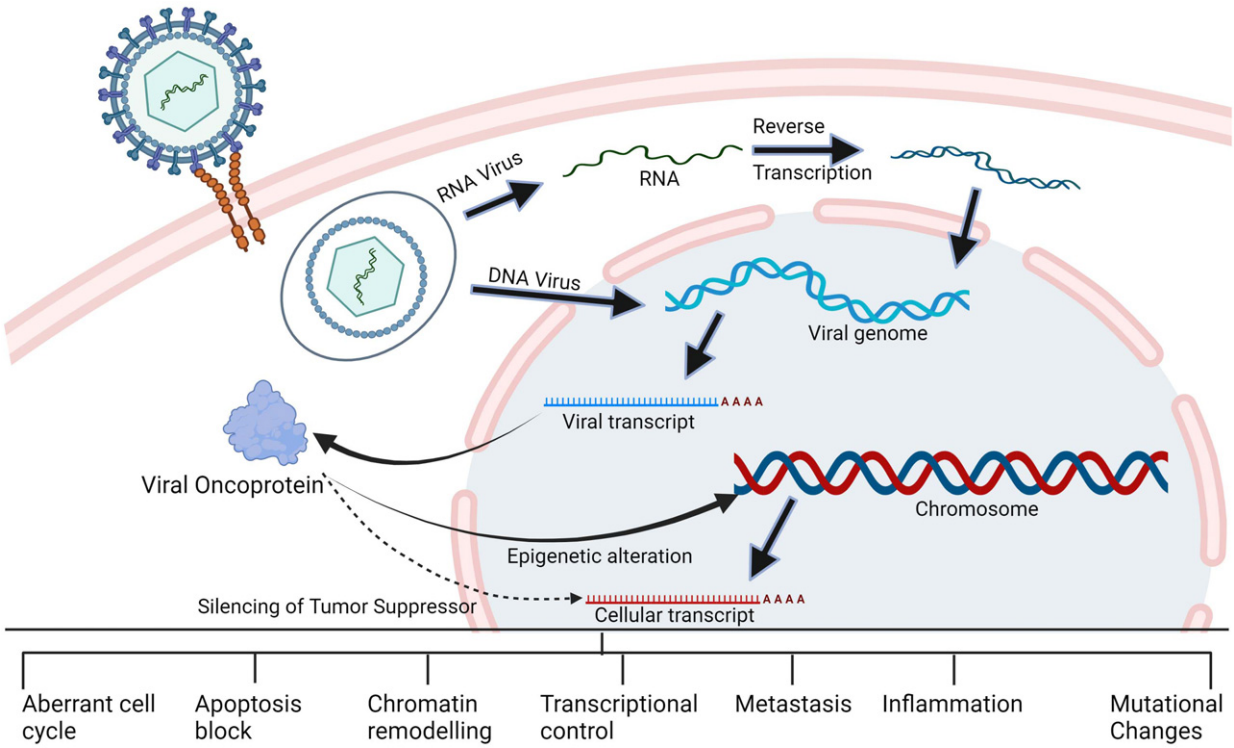


Fig. 1 Tumor virus infection induced immortalization of the infected cell through deregulation of critical cellular pathways like cellular signaling, cell-cycle control, and defense systems via expression of many potent oncoproteins (created with Biorender.com).

is essential to understand that viruses themselves are not the sole cause of human cancers. Instead, oncogenesis occurs following prolonged chronic infections, ultimately leading to cancer development (Mesri *et al.*, 2014). The initiation of the oncogenic processes is attributed to viral interactions with the human immune system and the subsequent suppression of the immune response.

It has been approximately 60 years since the initial discovery of a human virus, Epstein-Barr virus (EBV or HHV4), that can lead to cancer (Epstein *et al.*, 1964). Today, there are eight confirmed human cancer-causing viruses (White *et al.*, 2014), as listed in **Table 1**, and there are ongoing investigations into potential additional culprits. Here we explore the cancer-causing viruses, offering a comprehensive view of their commonalities and distinctions. Advances in technology since 1964 have allowed us to delve into the intricate interactions between viruses and their hosts at the molecular level. The realization that viruses can contribute to cancer has led to the development of two of the most effective anti-cancer vaccines targeting high-risk strains of human papillomaviruses (HPV) (Cheng *et al.*, 2020) and hepatitis B virus (HBV) (Chang, 2011). These vaccines have already had a dramatic impact on reducing the incidence of these cancers in human populations.

Characteristics of Virus Induced Cancers

Chronic viral infections are associated with cancers

The human cancer viruses exhibit the ability to establish long-lasting and persistent infections. In the case of certain viruses like EBV, it is widely believed that the infection persists throughout a person's lifetime and is prevalent in all human populations, becoming a part of our 'normal' viral flora. In the instances of HBV and HCV, it is probable that lingering infections contribute to chronic inflammation and cirrhosis, ultimately leading to liver cancer. However, these infections typically endure for many decades before the manifestation of cancer symptoms. The prolonged persistence of these viruses heightens the probability of developing secondary conditions that transform a latent viral infection into a symptomatic cancer. An example of this is observed in AIDS patients with Kaposi's sarcoma, where the loss of immunologic control over persistent KSHV infection often occurs decades after the initial infection (McLaughlin-Drubin and Munger, 2008; Schiller and Lowy, 2021).

Tissue tropism of oncogenic viruses

Neoplasia resulting from tumor viruses infection reflects their specific cell tropism. Some viruses exhibit highly specific cell targets, as seen in the case of HBV, which exclusively induces primary hepatocellular carcinoma without affecting other types of cancers. Likewise, HTLV-I infection leads to a distinct subtype of CD4 T-cell tumors known as adult T-cell leukemia, or adult T-cell leukemia/lymphoma when lymphomatous lesions are present in the skin. In contrast, high-risk human papillomaviruses are constrained to causing squamous epithelial cancers, albeit at various body sites, including the cervix, head-and-neck, and anus. These cancers are associated with sites of sexual transmission, encompassing heterosexual, orosexual, and anosexual activity. Conversely, both KSHV and EBV have diverse tissue reservoirs that can give rise to tumors. KSHV resides in endothelial and post-germinal B cells, causing endothelial Kaposi's sarcoma, B-cell primary effusion lymphoma, and B-cell lymphoproliferative syndrome. EBV, the most prevalent among human cancer viruses, exhibits the least restriction in the types of cancers it induces. It is not only linked to B-cell lymphomas but also associated with nasopharyngeal carcinoma, stomach cancer, T-cell lymphomas, and a rare form of leiomyosarcoma (**Table 1**).

In some tumors, a tumor virus is consistently present and essential for tumorigenesis, as exemplified by cervical cancer and Kaposi's sarcoma. However, more frequently, viruses contribute to only a subset of a particular tumor histotype. Although both HBV and HCV are implicated in the development of hepatocellular carcinoma, this form of cancer can also be initiated by factors like alcohol induced cirrhosis or exposure to dietary mycotoxins such as aflatoxin mutagen (Perz *et al.*, 2006). These environmental factors can act synergistically with HBV in the process of tumor development (Kirk *et al.*, 2006).

Variations in geographical conditions significantly influence the underlying epidemiology of viral cancers. All instances of Burkitt's lymphoma exhibit chromosome translocation between *c-myc* on chromosome 8 and one of the immunoglobulin loci on chromosome 14 (IgG heavy chain), chromosome 2 (kappa light chain), or chromosome 22 (lambda light chain), indicating the necessity of a cellular contribution to Burkitt's lymphomagenesis (Hartl and Lipp, 1987). In North American adults, including those with Burkitt's lymphoma in AIDS, fewer than 50% of tumors are positive for EBV. Conversely, in regions such as Papua New Guinea and sub-Saharan Africa, where malaria poses a risk factor for childhood Burkitt's lymphoma, EBV is almost universally present in the tumor cells.

Merkel cell carcinoma manifests as both MCV-positive (approximately 80%) and MCV-negative (approximately 20%) forms (Chang and Moore, 2012). MCV-positive tumors generally exhibit a somewhat less aggressive nature and greater responsiveness to therapy. Unlike MCV-negative tumors, MCV-positive tumors lack a consistent pattern of cellular mutations that would indicate a cellular driver mutation. In contrast, MCV-negative tumors display a pattern of widespread genomic mutations induced by ultraviolet light (UV) (Sihto *et al.*, 2009). It has been theorized that the carcinogenic impact resulting from an integrated and mutated MCV genomic structure is biologically equivalent to thousands of random genomic UV mutations, numbering up to 10,000 (Starrett *et al.*, 2017).

Table 1 Oncogenic viruses and associated cancers.

Virus	*Year of discovery*	*Virus classification and genome*	*Associated cancers*	*Other pathological diseases*	*References*
Epstein-Barr virus (EBV)	1964	Herpesviridae (180 KB linear dsDNA)	1. Burkitt's Lymphoma 2. Diffused Large B-cell lymphoma (DLBCL) 3. Hodgkin Lymphoma 4. Undifferentiated nasopharyngeal carcinoma 5. Gastric adenocarcinoma 6. Leiomyosarcoma 7. Post-transplant lymphoproliferative disorder (PTLD)	1. Infectious mononucleosis 2. X-linked lymphoproliferative syndrome 3. Multiple sclerosis 4. Oral hairy leukoplakia	(Epstein *et al.*, 1964)
Hepatitis B virus(HBV)	1965	Hepadnaviridae (3.5 KB circular dsDNA-RT)	Hepatocellular carcinoma	Hepatitis cirrhosis	(Blumberg *et al.*, 1965)
Human T-lymphotrophic virus 1 (HTLV-1)	1980	Retroviridae (9 KB ssRNA-RT, Positive strand)	Adult T-cell leukemia	HTLV1-myelopathy/ tropical spastic paraparesis	(Poiesz *et al.*, 1980)
Human T-lymphotrophic virus 2 (HTLV-2)	1982	Retroviridae (9 KB ssRNA-RT, Positive strand)	Adult hairyT-cell leukemia	Spastic myelopathy and variable degrees of ataxia	(Kalyanaraman *et al.*, 1982)
Human papilloma virus (HPV)	1983	Papillomaviridae (8 KB circular dsDNA)	1. Cervical carcinoma 2. Squamous cell head and neck carcinoma 3. Squamous cell anal carcinoma 4. Vulvar carcinoma	1. Benign genital leisons 2. Respiratory Papillomatosis 3. Oral focal epithelial hyperplasia	(Durst *et al.*, 1983)
Hepatitis C-virus (HCV)	1989	Flaviviridae (9.6 KB ssRNA-RT, Positive strand)	1. Hepatocellular carcinoma Lymphoma	Hepatitis cirrhosis	(Kuo *et al.*, 1989)
Kaposi sarcoma herpes virus (KSHV)	1994	Herpesviridae (145 KB linear dsDNA)	1. Kaposi Sarcoma 2. Primary effusion Lymphoma 3. Multicentric Castleman disease	KSHV inflammatory cytokine cyclone syndrome	(Chang *et al.*, 1994)
Merkel Cell polyoma virus (MCV)	2008	Polyomaviridae (5 KB circular dsDNA)	4. Merkel cell Carcinoma		(Feng *et al.*, 2008)

Virus induced oncogenesis is an indirect effect of viral infections

Oncogenic viruses do not inherently induce tumors as an integral aspect of their viral life cycles. All eight of these viruses are responsible for infections and can be transmitted without the majority of infected individuals developing neoplasia. While it may be tempting to hypothesize that the increasing mass of a tumor would contain more infectious virions, this is not the case, as viruses are typically present in a non-infectious form within tumors. It seems that viral cancers, akin to non-infectious cancers, arise as biological accidents. In the natural progression of the disease, resulting neoplasms are equally detrimental to the virus and its hosts. This poses an intriguing question: if viral oncogenes did not evolve to induce cancer for the benefit of the virus, why are they conserved? For many years, it was believed that these genes primarily induced an S-phase cell-cycle state to facilitate viral nucleic acid replication and suppressed apoptotic routines triggered by unscheduled cell-cycle entry (Levine, 2009). However, recent insights from innate immunology suggest that viral oncogenes may also function as immune evasion genes, preventing host cells from initiating stereotypical responses to infection, including cell-cycle arrest and programmed cell death (Moore and Chang, 2010).

Virion particles are absent in most of the tumor cells

Early investigations in tumor virology observed a distinctive characteristic of viral tumors, setting them apart from other viral diseases—namely, their general 'non-permissive' nature for replication within tumor cells (Zur Hausen, 2009). The active replication, known as lytic replication, of viruses triggers host immune responses that result in the death of infected cells, producing the well-known cytopathic effect. However, in viral tumors, viruses remain in a nearly silent state within each tumor cell, referred to as latency. During this latency, they either produce viral oncoproteins or initiate insertional mutagenesis, propelling tumor cell proliferation. The potential exception to this trend is hepatocellular carcinoma induced by HCV. The significance of non-permissivity to tumorigenesis is evident with HPV, HBV, and MCV—agents that typically do not form tumors unless mutations and integration events occur, rendering it impossible for the virus to actively replicate ('pseudolatency'). In the case of EBV and KSHV, the viruses remain latent in most cancer cells, resulting in no generation of infectious particles from the bulk of tumor cells. Replication may occur in a minor fraction of tumor cells, producing infectious virions but leading to the demise of the initiating tumor cells. This principle is harnessed by viral oncolytic therapies, which target specific tumors with defects in dual immune-tumor suppressor signaling pathways absent in healthy surrounding tissues. This makes some tumors particularly susceptible to viral lytic infection, leading to the induction of an effective anticancer immune response (Guo *et al.*, 2017).

Non-infectious cofactors contribute to virus induced oncogenesis

Individuals outside the field of epidemiology may find viruses as causative agents of cancer perplexing, given that most of these infections do not result in tumors. Infectious disease experts have long understood that many infections, except for specific cases like rabies virus, smallpox virus, and HIV, often manifest as asymptomatic and consequently go unnoticed. Non-infectious factors, including age, genetics, environmental conditions, and prior immunity, largely determine whether exposure to a virus leads to disease. This principle applies equally to infectious cancers. As previously mentioned, immunodeficiency is a significant factor in determining whether a tumor virus infection progresses to cancer. In the case of certain tumor viruses, host mutations predispose individuals to tumor formation after infection, as observed in genes encoding EVER1 and EVER2 for beta HPV-related epidermodysplasia verruciformis (Hufbauer and Akgul, 2017), or in SH2D1A for EBV-related X-linked lymphoproliferative disorder (Veillette *et al.*, 2013). Conversely, environmental exposures, such as dietary aflatoxin for HBV-related hepatocellular carcinoma (Kirk *et al.*, 2006) and malaria in childhood Burkitt's lymphoma (Moormann and Bailey, 2016), increase the risk of tumor development following exposure to tumor viruses.

Immune evasion of virus induced tumors

Almost all viral cancers documented to date show an increased incidence among immunosuppressed individuals (Grulich and Vajdic, 2015). This is particularly noticeable for viruses that directly transform cells (HTLV-I, HPV, MCV, EBV, and KSHV) through the expression of foreign oncogenes. As a result, cancer registry studies involving AIDS and transplant patients have played a crucial role in pinpointing potential infectious cancers, directly contributing to the identification of tumor viruses, including KSHV (Beral *et al.*, 1990) and MCV (Engels *et al.*, 2002). Additionally, aging is linked to more subtle immune dysfunctions, and several tumors with viral origins are associated with advanced age.

Epstein Barr Virus

EBV (Epstein-Barr virus) is the first confirmed human oncogenic virus, and after more than half a century of research, there is a detailed understanding of its pathogenic mechanisms. Approximately 95% of individuals harbor a lifelong, asymptomatic EBV infection, persisting within the memory B cell pool. Disruption of the equilibrium between the host and viral infection can lead to EBV-associated tumors, with B cell lymphomas being the most commonly observed (**Table 2**). EBV is a virus with a double-stranded DNA genome of approximately 184 kb, belonging to the human herpesvirus gamma subfamily. The genome of EBV encodes six nuclear antigens, namely EBNA1, 2, 3A, 3B, 3 C, and LP. Additionally, it encodes two membrane proteins, namely LMP1 and LMP2, as well as non-protein coding small RNAs (EBERs) and microRNAs (miRNAs).

Table 2 EBV genes and related pathogenesis.

Disease	*Cell origin*	*Associated markers*	*Correlation (EBV%)*	*References*
Infectious mononucleosis	B cells	Adults with primary infection face an increased risk of lymphoma.	100	(Sylvester *et al.*, 2023)
Lymphomatoid granulomatosis	B cells	Perivascular formation of granulomas by lymphocytes and large atypical cells.	100	(Roschewski and Wilson, 2012)
Nasopharyngeal carcinoma	Epithelial cells	EBV DNA, VCA-IgA, EBER	100	(Chen *et al.*, 2019a)
Burkitt lymphoma	B cells	EBNA1, EBERs (latency I)	>90	(Pannone *et al.*, 2014)
Endemic Burkitt lymphoma	Germinal center, Centroblast	Equatorial Africa, New Guinea	100	(Quintana *et al.*, 2020)
Sporadic Burkitt lymphoma	Germinal center, Centroblast	EBNA1	10–80	(López *et al.*, 2022)
HIV-related Burkitt lymphoma	Germinal center, Centroblast	EBNA1	30–40	(López *et al.*, 2022)
Post-transplant lymphoproliferative disorder	Initial or memory B cells	EBNA1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3 C, EBNA-LP, LMP1, LMP2	>90	(Atallah-Yunes *et al.*, 2023)
HIV-related lymphoproliferative disorder	B cells	Immunodeficiency-related, All EBNAs, LMPs	>90	(Vaccher *et al.*, 2022)
Classical Hodgkin lymphoma	Post-germinal Center, Centroblast	EBNA1, LMP1, LMP2	50–80	(Brice *et al.*, 2021)
Nodular sclerosis Hodgkin lymphoma	Post-germinal Center, Centroblast	EBNA1, LMP1, LMP2	10–40	(Wang *et al.*, 2021b)
Mixed cellularity Hodgkin lymphoma	Post-germinal Center, Centroblast	EBNA1, LMP1, LMP2	70–80	(Ansell, 2020)
Lymphocyte-depleted Hodgkin lymphoma	Post-germinal Center, Centroblast	EBNA1, LMP1, LMP2	10–50	(Ansell, 2020)
Rich in lymphocytes Hodgkin lymphoma	Post-germinal Center, Centroblast	EBNA1, LMP1, LMP2	30–60	(Ansell, 2020)
HIV-related lymphocytes Hodgkin lymphoma	Post-germinal Center, Centroblast	EBNA1, LMP1, LMP2	>90	(Behler and Kaplan, 2006)
NOS diffuse large B-cell lymphoma	Post-germinal Center, Centroblast	EBNA1 EBNA-2 EBNA-3A EBNA-3B EBNA-3 C EBNA-LP LMP1 LMP2	10	(Yenamandra *et al.*, 2022)
PAL diffuse large B-cell lymphoma	Post-germinal Center, Centroblast	EBNA1 EBNA-2 EBNA-3A EBNA-3B EBNA-3 C EBNA-LP LMP1 LMP2	100	(Liu *et al.*, 2022a)
Plasmacytic lymphoma	Primary plasmablast	-EBNA1	75–90	(Xie *et al.*, 2016)
Chronic active Epstein–Barr virus (CAEBV) disease	T/NK/B cell	Children; adolescents	100	(Kimura and Cohen, 2017)
Peripheral T-cell lymphoma	T cells	–	30	(Wang *et al.*, 2021a)
Extranodal NK/T-cell lymphoma	T/NK cells	-EBNA1 LMP1 LMP2	100	(de Leval *et al.*, 2023)
Invasive NK cell lymphoma	T/NK cells	–	100	(Wang *et al.*, 2021a)
Invasive NK cell leukemia	NK cells	Adults; Asia	>90	(Wang *et al.*, 2021a)
Severe mosquito bite allergy	T/NK cells	East Asia	100	(Quintanilla-Martinez *et al.*, 2023)
EBV-associated hemophagocytic lymphohistiocytosis	$CD8^+$ T/NK cells	Genetic defects	100	(Quintanilla-Martinez *et al.*, 2023)
Pediatric systemic EBV-related T-cell lymphoma	T cells	East Asia	100	(Quintanilla-Martinez *et al.*, 2023)
Pemphigoid-like EBV-positive T-cell proliferative disease	$\gamma\delta$T/NK cells	Asia; North America	100	(Quintanilla-Martinez *et al.*, 2023)
Pityriasis alba	Epithelial cells	HIV-related	100	(Lin and Janniger, 2005)

The cellular mechanisms of EBV infection manifest in various forms, with latent infections categorized into four types: Type III latent infection, characterized by the expression of all viral genes, is often observed in healthy carriers of EBV, post-transplant lymphoproliferative disorders (PTLD), HIV-associated immunoblastic lymphomas, and B cells of certain diffuse large B-cell lymphoma (DLBCL) patients; Type II latent infection primarily resides in germinal center B cells, expressing only EBNA1 and two latent membrane proteins, along with non-coding RNAs, and is associated with Hodgkin's lymphoma (HL); Type I latent infection transiently expresses the nuclear antigen EBNA1 and is observed in Burkitt lymphoma cells (BL); while Type 0 latent infection in memory B cells is characterized by the absence of EBV protein expression. Plasma cell differentiation can induce the production of infectious viral particles, a phenomenon observed in primary effusion lymphoma (PEL). Also, EBV induces host genome hypermethylation. Since the initial discovery of EBV in gastric cancer tissues in 1990, it has garnered widespread attention. It is estimated that approximately 25% of gastric cancer cases worldwide are associated with EBV infection, and this subtype of gastric cancer is termed EBV-associated gastric cancer (EB-VaGC) (Atri-Schuller *et al.*, 2022).

EBV-Associated Lymphomas

EBV was first isolated from endemic Burkitt's lymphoma (eBL) tissue in 1964 (Epstein *et al.*, 1964), and subsequently, epidemiological associations with Burkitt's lymphoma (BL) development were established (Geser *et al.*, 1982). Burkitt's lymphoma (BL) is a highly aggressive B-cell non-Hodgkin lymphoma characterized by its high malignancy, rapid clinical progression, and poor prognosis. eBL is the most prevalent subtype among pediatric lymphomas in sub-Saharan Africa, constituting the vast majority of cases. The progression of BL is closely associated with EBV infection. In sub-Saharan Africa, individuals typically acquire EBV around the age of 2, while in the northern hemisphere, infection commonly occurs during adolescence and early adulthood (de-The, 1977). Those infected with EBV carry the virus throughout their lifetime. EBV infects epithelial cells, usually in the nasopharynx, where it establishes a lytic infection, and B cells, where it establishes persistent latent infection (Young and Rickinson, 2004). In vitro, EBV-infected B cells undergo transformation and proliferate indefinitely as lymphoblastoid cell lines (LCL). During latency, the viral genome is maintained as an episome in the nuclei of B cells, with only a few viral genes being expressed. These genes can interfere with normal cellular signaling pathways.

Latent membrane proteins (LMP) 1 and 2 are expressed on the cell membrane of EBV-infected B cells, driving their proliferation and differentiation by mimicking signals received by normal B cells during the germinal center reaction. LMP1 acts as a constitutively active CD40 signal (Uchida *et al.*, 1999), and LMP2 as a constitutively active B-cell receptor signal (Mancao *et al.*, 2005). Other intracellular latent genes include EBNA1, EBNA2, EBNA3A-C, EBNA-LP, and two virally encoded small RNA transcripts, EBERs. The expression pattern of EBV latent genes is tightly regulated. After primary B cells become infected with EBV, LMP1 and LMP2 drive B cell proliferation and differentiation (Klein *et al.*, 2007).

EBV-infected B cells expressing the full repertoire of EBV latent genes are highly immunogenic, eliciting a robust cytotoxic T-cell response that ultimately opposes B cell proliferation. Simultaneously, the EBV latent program switches to a restricted pattern, leading to infected B cells acquiring a memory phenotype and harboring EBV with a highly restricted pattern of gene expression. These cells constitute the reservoir of EBV infection and persist throughout the lifetime of the infected individual. Occasionally, EBV-infected memory B cells are induced to differentiate into plasma cells, triggering the lytic program (Laichalk and Thorley-Lawson, 2005). Three distinct types of EBV latency programs occur in EBV-associated lymphomas (Kelly *et al.*, 2006). In immunodeficiency-associated lymphomas (posttransplant lymphoproliferative disorders and HIV-associated lymphomas in severely immunocompromised patients), type III latency is observed, closely resembling that seen in vitro in LCL, where most latent genes are expressed and drive B cell proliferation (Kempkes and Robertson, 2015). In EBV-associated Hodgkin's lymphoma, a more restricted type II latency is observed, with the expression of LMP1 and LMP2 contributing to the survival of malignant cells. EBV is universally associated with eBL, where a restricted type I latency is observed, similar to that seen in EBV-infected memory B cells in healthy carriers (Kalla and Hammerschmidt, 2012). A minority of sporadic BL (sBL) and immunodeficiency-associated BL (iBL) cases are also associated with EBV infection and exhibit a type I latency. During type I latency, only EBNA1 is expressed. Despite the association of eBL with EBV infection for over 50 years, the precise oncogenic role of the virus remains elusive. EBNA1 itself is not directly oncogenic but may exert an antiapoptotic role contributing to the malignant phenotype (Kelly *et al.*, 2006). Nevertheless, the ubiquitous presence of EBV in eBL cells, along with experimental evidence, suggests a pathogenic role of EBV in the development of eBL. EBV may cooperate with c-MYC in BL and may provide at least part of the antiapoptotic machinery required for cells that overexpress deregulated c-MYC.

The oncogenic role of EBV was confirmed in diffuse large B-cell lymphoma (DLBCL). In 2016, the World Health Organization (WHO) classified EBV-related diffuse large B-cell lymphoma (EBV-positive DLBCL, NOS) as a new subtype of DLBCL (Swerdlow *et al.*, 2016). With the continuous advancement of high-throughput sequencing technologies, comprehensive and effective genomic studies of EBV-positive DLBCL have been achieved. These studies have propelled our understanding of EBV-positive DLBCL into a new phase. The study by Kataoka *et al.* confirms that EBV-negative and EBV-positive DLBCL exhibit a similar quantity of copy number alterations (CNA). However, in comparison to EBV-negative DLBCL, EBV-positive DLBCL demonstrates a higher number of structural variations (SV) in terms of genomic alteration (Kataoka *et al.*, 2019). In EBV-positive DLBCL, the most frequently mutated gene is c-MYC, which exhibits overexpression in EBV-positive DLBCL and is associated with the International Prognostic Index (IPI) score. This suggests an unfavorable prognosis (median overall survival: 16 months vs. 29 months, $P < 0.01$). TET2 and DNMT3A exhibit a high frequency of mutations in EBV-positive DLBCL, suggesting a potential association between EBV infection and dysregulation of DNA methylation and demethylation processes (Zhou *et al.*, 2019).

The gene expression profile of EBV-positive DLBCL is characterized by the activation of the NF-kB and JAK-STAT pathways (Kato *et al.*, 2014). It has been reported that EBV gene products, such as LMP1, activate the NF-kB pathway in a ligand-dependent manner and impede the p16 (encoded by CDKN2A)-Rb pathway (Kato *et al.*, 2014). Using high-throughput sequencing, Kataoka *et al.* identified a markedly elevated frequency of mutations in TET2 and DNMT3A, alongside a significantly reduced frequency of mutations in CD79B, MYD88, CDKN2A, and FAS, in EBV-positive DLBCL. Simultaneously, this also elucidates the absence of mutations in CD79B, MYD88, and CDKN2A in EBV-positive DLBCL (Kataoka *et al.*, 2019). 66.7% of EBV-positive DLBCL displays positive pSTAT3, indicating the involvement of EBV in the activation of the JAK-STAT pathway (Teoh *et al.*, 2019). Furthermore, 44.5% of EBV-positive DLBCL exhibits co-expression of pSTAT3 and c-MYC, suggesting an association between alterations in the c-MYC gene and activation of the JAK-STAT pathway (Teoh *et al.*, 2019). Xiaoqiu Li et. al. found that EBV-positive DLBCL showed significantly lower expression of CIITA and MHC II compared to EBV-negative DLBCL (Jiang *et al.*, 2020). EBV-positive DLBCL exhibits heightened expression of the T-cell inhibitory ligand programmed death ligand 1 (PD-L1) (Jiang *et al.*, 2020). This results in the disruption of the antigen capture and presentation system, along with the co-option of the T-cell inhibitory molecule. These alterations potentially play a role in immune evasion within the context of this high-risk disease (Jiang *et al.*, 2020). Presently, PD-L1 is an immunotherapeutic checkpoint of significant therapeutic importance. The upregulation of PD-L1 serves as a mechanism for evading anti-tumor T-cell responses in various cancers. A large-scale study (n = 1557) found that 16% and 41% of patients with EBV-positive DLBCL exhibited PD-L1 expression in tumor cells and the microenvironment, respectively (Hu *et al.*, 2017; Kiyasu *et al.*, 2015). Additionally, preclinical research suggests that the blocking effect of PD-L1 is associated with the restoration of T-cell proliferation and activation in PD-L1-positive EBV-positive DLBCL (Zheng *et al.*, 2019). Therefore, targeting the PD-L1 pathway may emerge as a potential immunotherapeutic approach for EBV-positive DLBCL.

Post-transplant lymphoproliferative disorder (PTLD) is a group of lymphoproliferative disorders ranging from benign to malignant proliferation of the lymphatic system that occurs in patients after solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT) due to immunosuppression. The onset of PTLD is associated with recipient immune suppression and EBV infection. Approximately 50% to 70% of PTLD cases are linked to EBV infection, and in the context of HSCT, the occurrence of PTLD is almost invariably associated with EBV (Romero *et al.*, 2019). EBV remains latent within the recipients of SOT, and on switching to an immunosuppressed state the transplant recipient undergoes reactivation, subsequently infecting B cells. The pathogenesis of EBV-associated PTLD remains unclear. Currently, it is believed that immune dysfunction mediated by EBV-specific T cells plays a crucial role in the onset of the disease. The differences between EBV negative PTLD and EBV positive PTLD lie significantly in somatic mutations and TP53 gene alterations (Ferla *et al.*, 2020). Additionally, genomic analysis reveals distinctive pathogenic mechanisms for EBV negative PTLD compared to EBV positive PTLD. Nevertheless, the mechanisms leading to lymphoma development in EBV negative PTLD are analogous to those observed in individuals with intact immune function (Martinez and Krams, 2017; Courville *et al.*, 2016). Formerly, it was believed that post-SOT associated PTLD predominantly occurs within the first year post-transplant, with most cases being associated with EBV infection. In late-onset PTLD (occurring one year or more after transplantation), EBV negative PTLD constitutes a higher proportion compared to the early onset cases (Zaffiri *et al.*, 2020). A study conducted in France focusing on post-renal transplant recipients with PTLD and with a follow-up period extending up to 10 years revealed a bimodal onset pattern for EBV positive PTLD (Shahid and Prockop, 2021). The first peak occurred within the initial year post-transplantation, while the second peak was observed between 8 to 10 years post-transplantation. The study posited that the second incidence peak of EBV positive PTLD is associated with prolonged use of immune-suppressive agents (Taylor *et al.*, 2005). However, further research is required to elucidate the pathogenic mechanisms of PTLD and the role of EBV infection therein, facilitating improved prevention, diagnosis, and treatment strategies for post-solid organ transplantation associated PTLD.

Hodgkin's lymphoma (HL) is a type of B-cell lymphoma characterized by the presence of abundant Reed-Sternberg (R-S) cells and varying degrees of lymphoid tissue fibrosis. In 1832, Thomas Hodgkin reported 7 cases of tumor-like lesions in primary lymphoid tissue. It wasn't until 1987 that Weiss *et al.* first documented the detection of EBV in tissues removed from lesions in HL patients, providing evidence of the association between HL occurrence and EBV infection (Weiss *et al.*, 1987). The mechanistic role of EBV in the pathogenesis and progression of HL remains incompletely understood. However, research indicates that viral-encoded proteins such as LMP1 and LMP2 play crucial roles in the pathogenic mechanisms (Vockerodt *et al.*, 2008; Vockerodt *et al.*, 2013). Among these, there is a considerable body of research on LMP1. LMP1 can activate cellular signaling pathways, including NF-κB, JAK/STAT, and PI3K, and induce transcription activation of germinal center B cells (Vockerodt *et al.*, 2008; Ma *et al.*, 2022). In a study conducted by Souza *et al.* encompassing 97 HL patients treated at a Brazilian hospital from 1994 to 2004, the detection rate of EBV in patients was 52.5% (Martins *et al.*, 2022). Following EBV infection, the expression of EBNA-1, LMP, and EBER was observed, with high expression of LMP1. LMP1 activation of CD40 was noted, promoting enhanced transcription of the NF-κB signaling pathway, thereby contributing to the onset of HL (Ma *et al.*, 2017). Additionally, LMP1 was found to modulate IL-10, induce the production of interferon-γ, and regulate other cytokines, suppressing the generation of cytotoxic T lymphocytes (CTLs) and evading immune surveillance. These findings suggest a significant role for LMP1 in the pathogenic processes of Hodgkin's lymphoma (Souza *et al.*, 2010). The study by Yamamoto *et al.* revealed that in HL, the distinctive Reed-Sternberg (R-S) cells employ pathogenic mechanisms such as amplification of 9p24.1 and EBV infection to induce high expression of programmed death ligand (PD-L) 1 and PD-L2. This, in turn, leads to the binding of programmed death receptor (PD)-1 on T cells, ultimately inhibiting further activation, proliferation, and cytokine production by T cells. This immune evasion leads to the formation of tumor cells in Hodgkin's lymphoma (Yamamoto *et al.*, 2008). Based on the explanations provided by this study regarding the pathogenic mechanisms of HL, PD-1/PD-L1 inhibitors have emerged as novel therapeutic agents for HL. Nivolumab has received

approval from the United States Food and Drug Administration (FDA) for the treatment of relapsed or refractory Hodgkin lymphoma (R/RHL) (Kasamon *et al.*, 2017). Pembrolizumab has also been approved by the FDA for use in R/RHL that has failed three lines of treatment or more, or relapsed/refractory primary mediastinal large B-cell lymphoma following at least two prior treatment failures (Tomassetti *et al.*, 2019). The first domestically produced PD-1 monoclonal antibody, Camrelizumab, has been approved for use in R/RHL following at least second-line systemic chemotherapy (Merryman and LaCasce, 2019).

EBV-Associated NK and T-Cell Lymphomas

Extranodal NK/T-cell lymphoma (ENKTCL) is a relatively uncommon type of non-Hodgkin lymphoma characterized by local destruction of small blood vessels, tumor cells inducing focal tissue coagulative necrosis, and the expression of cytotoxic molecules along with EBV infection. The incidence of ENKTCL exhibits a distinctive geographical distribution, being more prevalent in Asia and certain South American countries, while being less common in Europe and North America. The male-to-female ratio ranges from 2 to 3.3:1, with an average age of onset between 45 and 50 years (Montes-Mojarro *et al.*, 2021). Typically, initial manifestations involve the nasal cavity or nasopharynx, with potential involvement in other sites such as tonsils, gastrointestinal tract, skin, and testicles. EBV viral infection was detected in more than 90% of the ENKTL patients with nasal cavity or nasopharyngeal (Asano *et al.*, 2013). EBV infection plays a pivotal role in the progression of ENKTCL. EBV infection in the host can be classified into latent infection and proliferative infection. In the case of ENKTCL patients, latent infection is more common. Following EBV infection, the expression of a series of latent proteins is closely associated with pathogenesis, with particular emphasis on the significant role played by LMP1 in the occurrence and progression of ENKTCL.

Over the past two decades, extensive and comprehensive research has been conducted on the proliferative mechanisms of ENKTCL. The JAK/STAT signaling pathway plays a pivotal role in the development of ENKTCL, as revealed by comprehensive research (Bouchekioua *et al.*, 2014; Coppo *et al.*, 2009). Analysis of the Gene Expression Profile (GEP) data has uncovered significant upregulation of genes on the JAK/STAT pathway in ENKTCL compared to normal NK cells (Lee *et al.*, 2015). According to reports, the constitutive activation of the JAK/STAT pathway in ENKTCL is primarily attributed to abnormal mutations in JAK3, STAT3, and STAT5, with the mutation frequency ranging from 0% to 35% (Lee *et al.*, 2015; Kimura *et al.*, 2014; Koo *et al.*, 2012). Another study indicated the presence of STAT3 phosphorylation in 87% of ENKTCL cases, with only 20% resulting from kinase domain-activating mutations. Several similar studies have demonstrated that mutations in STAT3 and STAT5 genes are uncommon in ENKTCL, with alterations primarily involving phosphorylation changes in STAT3 in most cases (Küçük *et al.*, 2015).

In the study of the Gene Expression Profile (GEP), it was observed that the expression of NF-κB-related genes in ENKTCL is relatively increased (Iqbal *et al.*, 2011). Research has revealed the involvement of NF-κB in the pathogenesis of phagocytic cells, constituting a pivotal factor in the mortality of ENKTCL patients (Wen *et al.*, 2018). The endoplasmic reticulum (ER) stress-inducible transmembrane (ER-stress inducible transmembrane, ECSIT) protein is a cytoplasmic protein that exhibits evolutionarily conserved characteristics in Toll-like receptor 4 (TLR4)-mediated activation of the NF-κB signaling pathway (Wi *et al.*, 2014). Additionally, individuals with Natural Killer/T-cell lymphoma ENKTCL often carry mutations in ECSIT-T419C, a mutation that can activate the NF-κB pathway. This activation leads to the release of pro-inflammatory cytokines, including TNF-α and IFN-γ, thereby promoting the activation and phagocytosis of macrophages (Wen *et al.*, 2018). Similarly, through gene expression profiling (GEP), elevated expression of c-MYC has been identified in ENKTCL (Lee *et al.*, 2015). Although chromosomal translocation involving the c-MYC gene has not been confirmed in ENKTCL, immunohistochemical results demonstrating co-overexpression of c-MYC along with the anti-apoptotic protein BCL-2 have been proposed as adverse prognostic factors (Wang *et al.*, 2017). Furthermore, it is currently known that c-MYC serves as a transcriptional target of EBNA2 and LMP1. Therefore, predictions suggest that the upregulation of c-MYC in ENKTCL is mediated by EBV (Ng *et al.*, 2011). Bi *et al.* discovered that LMP1 activates the NF-κB and MAPK2 signaling pathways, promoting high expression of PD-L1 (Bi *et al.*, 2016). Binding to PD-1, PD-L1 inhibits the activation and proliferation of T lymphocytes, induces apoptosis, weakens the immune response in the host, leading to immune escape of diseased cells, and promoting the occurrence of ENKTCL. Based on this, drugs targeting the PD-1/PD-L1 signaling pathway have become a focal point in current anti-tumor therapy. Such drugs function by disrupting the binding between PD-1 and PD-L1, restoring T cell function, and thereby exerting anti-tumor effects (Bi *et al.*, 2016).

Aggressive NK cell leukemia (ANKL) is a proliferative neoplasm of natural killer (NK) cells, characterized by its rarity and geographic variation in incidence. It is not uncommon, with a higher prevalence observed in Asia, and is associated with a poor prognosis. ANKL is associated with EBV infection (Montes-Mojarro *et al.*, 2021). Ruskova *et al.* conducted a comprehensive analysis of 73 diagnosed ANKL patients, summarizing epidemiological, immunophenotypic, and cytogenetic aspects. Among these cases, 34 patients were confirmed to have EBV infection, establishing an association between ANKL and EBV. However, the pathogenic mechanisms remain unclear (Ruskova *et al.*, 2004). Angioimmunoblastic T-cell lymphoma (AITL) is an invasive T-cell lymphoma that originates from follicular helper T cells (TFH) in the germinal center. It is clinically rare, accounting for 2% of non-Hodgkin lymphomas (NHL), and is associated with a poor prognosis (Zing *et al.*, 2018). When the immune system is suppressed or disrupted, B cells carrying EBV can evade immune surveillance and escape clearance by the host immune system. As a result, EBV can be detected in the serum of the majority of AITL patients (Yap *et al.*, 2022). The present research shows that EBV infection of host B cells convey signals from EBV proteins such as EBNA1 and LMP1 to T cells through the major histocompatibility complex II (MHC II) (Huang *et al.*, 2023). The activated antigen-presenting cells upregulate the expression of CD28, and during this process of antigen presentation, both antigen and co-stimulatory signals further activate T cells. This activation leads to the secretion of the

chemokine CXCL13, promoting continuous activation and proliferation of follicular helper T cells (TFH). However, B cells infected with EBV can evade immune surveillance and avoid clearance by the host immune system. CXCL13, in turn, stimulates the activation and proliferation of B cells, creating a continuous loop of immune stimulation. Ultimately, TFH cells undergo sustained activation and proliferation, resulting in formation of an immunostimulatory environment. Consequently, TFH cells evolve into pathogenic cells, contributing to immune abnormalities and tumor development (Dunleavy *et al.*, 2007).

EBV and Gastric Cancer

Burke *et al.* first reported the association between EBV and gastric cancer in 1990. The study involved the detection of EBV DNA in rare lympho-epithelioma-like gastric carcinoma tissues (Burke *et al.*, 1990). In 1993, Japanese researchers led by Tokunaga identified tumors as Epstein-Barr virus-associated gastric carcinoma (EBVaGC) based on positive expression of EBER1. As these tumors expresses high EBER1, they detected it by in situ hybridization (EBER-ISH) (Yang *et al.*, 2020). Numerous studies have observed a significantly increased prevalence of EBV infection in remnant gastric cancer compared to ordinary gastric cancer, suggesting that remnant gastric cancer may serve as a predisposing condition for EBVaGC (Akiba *et al.*, 2008; Koriyama *et al.*, 2005; Murphy *et al.*, 2009). From the perspective of EBV infection patterns in EBVaGC, unlike B lymphocytes, epithelial cells lack the CD21 molecule or type II complement receptor (CR2) with high affinity for the EBV outer membrane glycoprotein gp350/220 (Wang *et al.*, 1998). This absence suggests that EBV may infect epithelial cells through specific pathways distinct from those utilized for B lymphocyte infection (Hutt-Fletcher, 2017). Currently, several theories are proposed regarding the modes of EBV infection in the gastric epithelium:

Direct contact infection

EBV, concealed in the oropharynx, enters the stomach with saliva and directly settles on the surface of gastric mucosal epithelial cells (Yang *et al.*, 2020; Chen and Longnecker, 2019).

Cell fusion infection

B lymphocytes infected with EBV fuse with epithelial cells, resulting in the infection of the epithelial cells. The viral membrane directly fuses with the host cell plasma membrane to promote entry into epithelial cells. (Fukayama, 2010; Miller and Hutt-Fletcher, 1992; Tsang *et al.*, 2014; Wu *et al.*, 2003). 2.4.3 EBV Interaction with Specific IgA and Secretory Component (SC): EBV effectively binds to gp350/220-specific SC. The latter is a transmembrane protein expressed on the surface of epithelial cell basement membranes. Subsequently, the EBV/IgA/SC complex infects epithelial cells through endocytosis (Sixbey and Yao, 1992; Su *et al.*, 2023). NPC patients exhibit heightened levels of IgA against EBV-specific antigens in their mucosal secretions (Wu *et al.*, 2003; Tsang *et al.*, 2014). EBV entry into nasopharyngeal epithelial cells in vivo might occur through a specific mechanism involving EBV-IgA-SC-mediated endocytosis, indicating a physiological pathway for viral entry.

Infection with recombinant EBV containing gH/gL attachments

Some recombinant EBV, after infecting B lymphocytes, contains gH/gL attachments that can specifically bind to epithelial cells lacking CD21 molecules, leading to the infection of epithelial cells. Research also indicates that the interaction of gH/gL with integrins αVß6 and αVß8 facilitates EBV infection of epithelial cells (Chesnokova and Hutt-Fletcher, 2011).

Interaction of EBV membrane protein BMRF2 with integrins

EBV-encoded membrane protein BMRF2 interacts with integrins on the surface of epithelial cells, forming a tripeptide motif (Arg-Gly-Asp, RGD) (Xiao *et al.*, 2007). This interaction facilitates the attachment of EBV to the surface of epithelial cells (Xiao *et al.*, 2008). Shannon-Lowe *et al.* demonstrated that the incorporation of both RGD peptides and KGD peptides has been observed to effectively inhibit EBV infection by up to 40% (Shannon-Lowe and Rowe, 2011). These research underscored the significance of integrins present on the surface of human epithelial cells in facilitating EBV infection. The pathway utilized depends on various factors, including the expression of relevant EBV receptors.

EBV and Nasopharyngeal Carcinoma

In 1980, the first evidence of the association between EBV infection and nasopharyngeal carcinoma (NPC) was discovered. Elevated titers of EBV antibodies, including antibodies against viral capsid antigen (VCA) and early antigen (EA), were identified in the serum of nasopharyngeal carcinoma patients. Subsequently, the presence of the EBV genome in NPC cells was confirmed using in situ hybridization (McKenzie and El-Guindy, 2015). Edward *et al.* discovered that the EBV infection rate was 81.7%, with infection rates of 44.4% in early (Stage I + II) and 88.2% in advanced (Stage III + IV) stages of NPC. The incidence of EBV infection increased with later stages, with higher EBV-DNA quantification associated with advanced stages. Elevated EBV-DNA levels were indicative of poor prognosis, higher tumor burden, and EBV-DNA positivity served as a marker for predicting the long-term prognosis of NPC (To *et al.*, 2003). Typically, EBV remains in a latent infection in B cells which can support B cell proliferation and immortalization. However, in epithelial cells, EBV infected primary nasopharyngeal epithelial cells can lead to growth arrest (Feederle *et al.*, 2007). Many studies have found that LMP-1 plays an important role in the development of EBV-

associated NPC. LMP-1 induces morphological changes in fibroblasts and unrestricted cell proliferation in primary B cells and human epithelial cells. This leads to the loss of contact inhibition, malignant transformation, and acquisition of oncogenic properties, classifying LMP-1 as an oncogene. Some in vivo research demonstrate that LMP-1 significantly alters the biological characteristics of NPC tissues, exerting an influence on the morphology and differentiation of NPC tissue (Lao *et al.*, 2019). Additionally, 26% of tumors express high levels of LMP1, which is a well-known activator of the NF-κB pathway in NPC (Li *et al.*, 2017). Past studies have indicated that the p50/p50/BCL3 complex is a major NF-κB signaling pathway in NPC (Thornburg *et al.*, 2003). The deubiquitinase (DUB) encoded by CYLD can regulate the nuclear aggregation of BCL3. The frequent somatic alterations in CYLD (18.6%) in NPC further support the crucial role of constitutive activation of this atypical NF-κB signaling in the development of NPC (Massoumi *et al.*, 2006).

Treatment for EBV Infections

Primary EBV infection typically doesn't show symptoms, but some individuals develop infectious mononucleosis, which can range from mild symptoms like fever, sore throat, and swollen lymph nodes to severe cases that can be life-threatening in immunocompromised individuals. Corticosteroids are commonly used to treat complications associated with infectious mononucleosis. While the effectiveness of antiviral medications in managing severe complications of infectious mononucleosis is a topic of debate based on case studies, healthcare providers may consider using antiviral drugs for severe EBV infections. EBV lytic replication is not only linked to infectious mononucleosis but also to conditions like chronic active EBV infection (CAEBV) and oral hairy leukoplakia. Various treatments, including immunomodulatory agents like interferon-α and interleukin-2, antiviral drugs such as acyclovir, ganciclovir, and vidarabine, chemotherapy, EBV-specific cytotoxic T lymphocytes cell therapy, and hematopoietic stem cell transplantation, have been attempted for CAEBV treatment but have shown limited success (Wass *et al.*, 2018).

Post-transplant lymphoproliferative disorder (PTLD) is a severe and frequently fatal complication that can occur after solid organ transplantation, with EBV being a significant risk factor for PTLD development. Historically, antiviral therapy was not considered effective against PTLD due to the virus being in a latent state. However, administering antiviral drugs prophylactically has led to a decreased incidence of PTLD (Hocker *et al.*, 2012). Strategies targeting the suppression of lytic protein expression are expected to be beneficial in managing the initial phases of EBV-related cancers, given that EBV lytic infection has been demonstrated to play a role in lymphoproliferative diseases (Hong *et al.*, 2005a). IL-6 is a cytokine that plays a critical role in maintaining immune functions, promoting the differentiation of hematopoietic cells, and sustaining inflammation. However, it also serves as a significant factor in various hematological and epithelial cancers. IL-6 functions through paracrine and autocrine pathways to support cell survival and activate the signal transducer and activator of transcription 3 (STAT3). Therefore, it's not surprising that viruses like EBV, which can infect both epithelial and lymphoid cells, have mechanisms to trigger IL-6 expression. Additionally, cells infected with the virus during the lytic phase induce the expression of both cellular and viral IL-10 (Hong *et al.*, 2005b) which allows B-cells to grow efficiently thus contributing to angiogenesis in both B-cell and epithelial malignancies.

Hepatitis B Virus

Since 1963, when Blumberg and Alter first identified the Australia antigen in the blood of an Australian Aboriginal individuals, and in 1970 when Dane *et al.* discovered intact Hepatitis B virus (HBV) particles, human exploration of HBV has continued. Approximately 400 million people are currently chronically infected with HBV in the world. The role of HBV in liver diseases is obviously important. Chronic infection with HBV can lead to a series of severe liver conditions, including chronic hepatitis B, liver cirrhosis, and primary hepatocellular carcinoma (HCC) (Feitelson and Lee, 2007). The WHO categorizes HBV as a class 1 indirect carcinogen, ranking just below smoking (World Health Organization). Due to late-stage diagnoses and limited treatment options, HCC has become the third leading cause of cancer-related mortality, following only gastric and lung cancers. Furthermore, nearly 53% of HCC cases are associated with HBV infection. Many studies report that latent infection of HBV is a critically significant risk factor closely involved in the initiation and progression of primary liver cancer (Tsai *et al.*, 2018).

HBV Structure

HBV is a hepatotropic partially double-stranded DNA virus, and the genomes of hepatotropic viruses are generally quite small. The HBV genome is approximately 3200 base pairs in length. The full genome encodes various viral proteins, including surface proteins (S proteins – L, M, S), core protein, pre-core protein, polymerase protein (pol protein), and X protein. There is partial overlap between these four open reading frames, demonstrating the virus's efficient utilization of its own resources (Echeverría *et al.*, 2015). The S gene region: The S gene is located between nucleotide positions 155 and 832, with a length of 687 base pairs, encoding a membrane protein of 226 amino acids. The upstream region of the S gene comprises the preceding S1 gene and the preceding S2 gene, which encode the preS1 and preS2 antigens, respectively. The S gene region can encode three types of S proteins, large surface protein (LHBs), medium surface protein (MHBs), and small surface protein (SHBs) refer to three distinct forms of the viral surface antigen, collectively forming the envelope component of the HBV, known as HBsAg. Detection of HBsAg, preS1 or preS2 in serum indicates the presence of HBV replication in the body (Nicolini *et al.*, 2019). The C gene region including the C gene and the pre-C

gene. The length of C gene region is 639 base pairs, and the C gene within this region encodes the core membrane protein, namely HBcAg, serving as the structural protein of the viral nucleocapsid. The pre-C gene is 87 base pairs, encoding a 29-amino acid signal peptide for the precursor of hepatitis Be antigen (HBeAg). The HBeAg precursor is translated from the pre-C region and the C gene, generated through the translation of pre-C mRNA, followed by cleavage to produce HBeAg (Liu *et al.*, 2021a).

HBcAg is predominantly located within the cell nucleus, rendering it undetectable in peripheral serum. Antibodies induced against HBcAg lack neutralizing capabilities; however, research suggests its robust immunogenicity, making it a potential adjuvant in vaccines. Both HBcAg and HBeAg are integral components of HBV, representing the degree of viral replication and infectivity in clinical contexts. Furthermore, they can serve as prognostic indicators for predicting disease progression (Akbar *et al.*, 2013). The P gene region is the longest gene in HBV, including four segments: the N-terminal region, spacer region, polymerase region, and C-terminal region. This region encodes the DNA polymerase and RNase H domains, respectively. The P gene actively participates in the entire process of HBV replication. Detection of the P gene product in patient serum indicates ongoing HBV replication, signifying heightened infectivity (Mak *et al.*, 2017). The X gene region is the shortest gene in HBV, spanning nucleotide positions 1374 to 1835, with a length of 462 base pairs. It encodes the HBx protein, consisting of 154 amino acids. It is now understood that HBxAg serves as an intermediate product in HBV replication. While its presence in circulating blood is minimal, HBxAg plays a regulatory role in gene expression (Feitelson *et al.*, 2005). The S gene, C gene, and P gene collectively encode structural proteins of HBV (Zhao *et al.*, 2021a). Although HBeAg and HBxAg are not structural proteins of HBV, they serve as essential functional proteins required for the interaction between HBV and the host. During the process of HBV infection, numerous specific particles are generated, exhibiting three distinct morphologies visible under electron microscopy (Datta *et al.*, 2012). One type is large spherical particles (diameter 42 nm) with both an outer envelope and a core, representing intact HBV particles, also known as Dane particles. These Dane particles exhibit robust viability and infectivity. Another type is small spherical particles (diameter 22 nm), and the third type is filament particles (width 22 nm, length 40–100 nm), possibly originating from the concatenation of small spherical particles (Herrscher *et al.*, 2020).

Once virus enter the host cells, HBV undergoes a transition from relaxed circular DNA (rcDNA) to covalently closed circular DNA (cccDNA). This cccDNA forms a small chromosome composed of viral and cellular proteins, including histones and non-histone proteins. It serves as the template for the transcription of all viral mRNAs (Levrero *et al.*, 2009). During treatment with nucleoside analogs which can inhibit HBV replication, the cccDNA persists. Therefore, even after successful treatment and clearance of HBsAg, the disease may still have the potential for recurrence (Abu-Amara and Feld, 2013). The incidence of HCC in individuals who carrying the HBV is 25–37 times higher than that in uninfected individuals (Sun *et al.*, 2003). HBV can promote the development of HCC through various mechanisms (**Fig. 2**), including integration with the host genome, the maintenance of an inflammatory microenvironment, activation of carcinogenic pathways, induction of cellular mutations, and alteration of metabolic patterns.

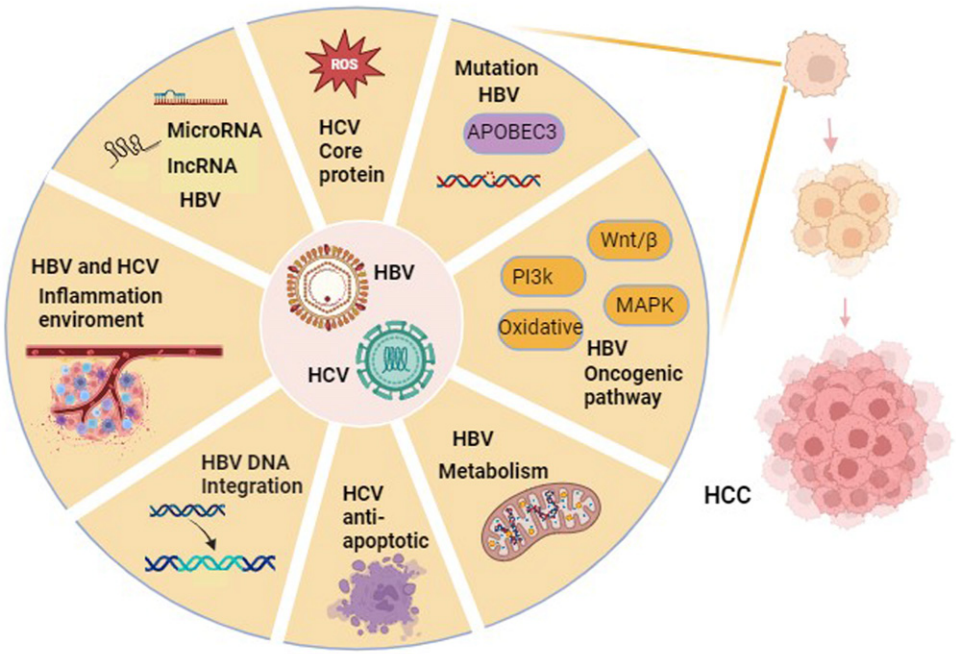


Fig. 2 The role of HBV and HCV virus in promoting the development of HCC.The role of HBV and HCV in promoting the development of HCC. Different risk factors caused by HBV in HCC progression, which are crucial for the development of targeted therapies and interventions to prevent or treat liver cancer. HCV induces inflammation environment and anti-apoptotic, blocks cell death, triggers persistent inflammation and ROS production, and dysregulates host lipid metabolism.

HBV DNA Integration

While integration is not strictly indispensable for virus replication, it does prolong the persistence of the viral genome. The process of viral DNA integration into the host genome is an important molecular mechanism which contribute to HCC occurrence. In 85% to 90% of HBV-related HCC cases, the presence of integrated viral DNA has been identified (Jiang *et al.*, 2021). Although HBV typically present in relaxed circular DNA (rcDNA) forms within host cells, the integration of HBV fragments into the host genome does not directly drive HBV replication. However, integrated HBV DNA can alter chromosomal stability, potentially activating various host genes and inducing alterations in the host genome. This activation is often instigated by the disruption of intact HBV DNA, leading to the synthesis of viral proteins and gene products that subsequently impact host cell function (Ringelhan *et al.*, 2013).

The occurrence of prolonged chronic inflammation significantly amplifies the abundance of viral free DNA fragments within the host DNA during cycles of continuous cell death and proliferation, consequently facilitating the process of viral integration. Notably, cellular topoisomerase I plays a pivotal role in the processes of viral linearization and integration replication. Various forms of alterations in the HBV genome sequence have been identified, with segmental duplications and deletions being prevalent. Factors such as exposure to oxidative stress or mutagens, impaired DNA repair capacity, inflammation, and co-infection with other viruses may contribute to HBV DNA integration (Ringelhan *et al.*, 2013). Under these circumstances, the genome becomes increasingly unstable, often resulting in segmental deletions, single or double-strand breaks, or rearrangements (Guerrero and Roberts, 2005).

Integration of HBV can induce recombination or deletion events in the vicinity of integration sites on the host chromosome (Lupberger and Hildt, 2007). Using HBV-ALU PCR, Paterlini-Bréchot *et al.* identified nine DNA integration regions from HCC cells, illustrating that the integration of viral genes into the host genome can lead to mutations in genes with significant regulatory functions (Paterlini-Brechot *et al.*, 2003). These genes, including interleukin-1-receptor-associated kinase 2 (IRAK2), tyrosine receptor kinase 2 (TYK2), inositol 1,4,5-trisphosphate receptor type 2 (IP3R2), MAP kinase isoform p42 (p42-mapk), intracellular ion channel inositol 1,4,5-triphosphate receptor (IP3R1), human telomerase reverse transcriptase (hTERT), and thyroid hormone protein gene, play crucial roles in cell proliferation, differentiation, and survival. Different genes integrated into distinct HBV DNA binding regions lead to specific functionalities, yet all induce abnormal changes in cellular signaling pathways. Additionally, HBV has been found to preferentially integrate into telomerase and IP3R in two different tumors (Paterlini-Brechot *et al.*, 2003), suggesting that viral integration may exhibit preferential regions, particularly in the case of the hTERT gene (Pollicino *et al.*, 2011).

Efficient integration of HBV into the human genome results in insertional mutations, exerting insertional selection pressure and thereby augmenting the carcinogenic potential for individuals with HBV infection. The primary integration sites for HBV are located on the MLL and hTERT genes (Murakami *et al.*, 2005). The proposed three distinct modes of activation of HBV DNA integration genes on chromosome 11q13 in the SNU cell line: (1) viral integration at integration sites causing gene changes without gene amplification, subsequently activating gene expression; (2) viral DNA-induced gene amplification, causing gene overexpression during integration and rearrangement; (3) activation of genes associated with gene amplification, regardless of whether viral integration occurs (Zhang *et al.*, 2006).

Advancements in sequencing method have expanded the scope of HBV DNA integration detection beyond conventional PCR-based techniques (Matsubara and Tokino, 1990). The emergence of affordable next-generation sequencing technology has enabled the extensive utilization of big-data analytics to comprehensively characterize HBV–host integration in HCC patients. The analysis of HBV integration in HCC patients by HBV probes and high-throughput sequencing indicated that integration breakpoints are dispersed across all gene regions of the virus. X, C, enhancer, and S genes was found to be integrated into the host genome from the HBV DNA sequences. Notably, the X and C genes stand out as the predominant integration genes within the genomes of HCC patients (Lee *et al.*, 2019). The integration of X gene fragments can directly induce HCC as viral oncogenes or indirectly activate proto-oncogenes or transcription factors within cells through encoded HBxAg, leading to the occurrence of HCC (Murakami, 2001). The expression of C-terminal truncated X protein (Ct-HBx) facilitates hepatocyte proliferation and reprograms cellular metabolism by suppressing thioredoxin-interacting protein (TXNIP) (Zhang *et al.*, 2021). Moreover, Ct-HBx regulates the transcription of Caveolin-1 and maintain the stability of LRP6, sustaining the activation of β-catenin. This contributes to the occurrence of HBV-associated HCC, amplifies the invasion, and fosters the metastasis of HCC cells.

HBV and Gene Mutation

HBV is more susceptible to mutation than other DNA viruses, which is related to the lack of proofreading function during reverse transcription of HBV pre-genomic RNA, which further leads to an increased risk of mutation in viral replication (Wang *et al.*, 2015). These mutations directly influence the development of HCC (Tatsukawa *et al.*, 2011). Chronic inflammatory reactions in hepatocytes due to HBV infection and reactive oxygen species production further damage HBV DNA, inducing gene mutations. Factors such as long-term HBV infection, host immune selection, antiviral and hepatitis B vaccine treatment, contribute to the generation of selective mutations, dominant mutations, and escape mutations. Mutations in HBV genes fundamentally influence the biological characteristics of the virus. They can alter the replication capacity, pathogenicity, antigenic epitopes, and resistance to antiviral drug treatments, contributing to persistent infection, severe hepatic damage, exacerbation of hepatocellular inflammatory responses, increased hepatocellular fibrosis, and an elevated risk of hepatocellular carcinoma (Jang *et al.*, 2012). This region encompasses two enhancers, EnhI and EnhII, as well as four promoters controlling HBV transcription, associated with DNA

synthesis and RNA virion encapsulation, and implicated in resistance to antiviral nucleotide analogs (NAs). Under the selective pressure of NAs, HBV gene mutations gradually accumulate during the replication cycle. Consequently, resistance to NAs is further selected and accumulates.

Point mutations, deletions, and base substitutions can occur in the PreS/S region. The PreS1 and S region gene promoters are correlated with mRNA translation (Caligiuri *et al.*, 2016). The PreS2 region gene is associated with HBV secretion and contains binding sites for B-cell and T-cell antigens, crucial for immune response activation (Chen, 2016). Research has identified mutation sites in the PreS/S region, which primarily include A826G, C531T, T667C, C512T, and C546A (Yin *et al.*, 2016). Accumulation of gene mutations in the PreS region gradually induces HBV DNA damage, ultimately leading to HCC (Liu *et al.*, 2022).

The PreC mutation region is the earliest and most frequently observed mutation in HBV, associated with serum conversion of HBeAg (Wu *et al.*, 2021). Major mutations in the PreC/C region include A1846T and G1896A, with the latter leading to termination of HBeAg expression, reducing anti-HBe production and possibly contributing to immune escape. Mutations G1613A and C1653T in the core promoter region affect chromatin precursor and PreC RNA, with G1613A inhibiting negative regulatory factor expression, subsequently influencing the proliferation and induction in expression of virus-related proteins, ultimately leading to HCC (Tatsukawa *et al.*, 2011). The C1653T mutation affects the expression of the H94Y protein in the X region, leading to substitution of histidine with tyrosine. Consequently, this alteration affects multiple intracellular signaling pathways, cellular proliferation, and apoptotic regulatory functions, thereby increasing the risk of HCC (Ito *et al.*, 2006). Research has also indicated that the C1653T mutation can enhance the activation of the EnhII/core promoter Box-a region, augmenting their affinity (Günther *et al.*, 1998). Many transcriptional regulatory factors are connected to nucleotide 1653, and the C1653T mutation can influence the affinity of these factors. Studies have demonstrated that C1653T serves as a predictive factor for HCC. Furthermore, C1653T can result in a significant elevation of alpha-fetoprotein (AFP), which holds guiding significance for the diagnosis and prognosis of HCC (Kim *et al.*, 2016).

Basal core promoter (BCP) mutations may contribute to the development of HCC through several potential mechanisms. First, overlapping regulation of the X open reading frame with PreC and C transcription in the BCP region: the BCP region overlaps with the X open reading frame, regulating the transcription of PreC and C regions. This regulation further influences the expression of PreC and RNAs of core proteins, subsequently affecting expression of HBcAg and HBeAg. This process reduces the levels of free HBeAg, which affects the clearance of HBV-infected liver cells and enhances immunotolerance, leading to sustained viral infection (Muñoz *et al.*, 2011). Second, the BCP and X open reading frames overlap, affecting amino acids K130M and V131I encoded by the X region, which are associated with cellular growth and DNA repair (Kim *et al.*, 2016). These changes may promote the progression to HCC. Consistency between codons 130 and 131 in the X region and the double mutation at positions 1762 and 1764 in the BCP region has been observed. BCP double mutations can increase HBV replication, enhance the host's immune response to infected liver cells, leading to liver cell apoptosis and regeneration, exacerbating liver damage, or altering the coding region of X (Xu *et al.*, 2011). The HBV X antigen coded within the X region transcriptionally activates the virus and host genes, and is closely related to P53 and DNA repair enzyme XAP-1 (Wang *et al.*, 2016). Third, the BCP region encodes the HBcAg protein, a strong antigen expressed on the surface of liver cell membranes. HBcAg is a crucial target for host immune response, inducing cytotoxic T lymphocyte reactions, especially CD4 and CD8 cells (Ye *et al.*, 2015). BCP mutations may lead to failure of activated cytotoxic T lymphocyte reactions or, by affecting HBeAg expression and viral replication, which contribute to sustained HBV infection (Wang *et al.*, 2016), leading to worsening liver cell damage and abnormal liver function. Related studies have found that joint mutations in EnhII/BCP can further increase the risk of HCC (Qu *et al.*, 2016).

HBV and MicroRNA

The majority of miRNAs inhibit HBV replication and expression through direct or indirect interactions with HBV transcription. Key miRNAs associated with HBV infection, mutual interactions with HBx, and HBV-related HCC include the miR-29 family, miR-199 family, miR-15/16 family, let-7a family, and miR-122 (Lamontagne *et al.*, 2015). miRNAs play a crucial role in the early detection of HBV infection, clinical diagnosis, disease progression, and prediction of HCC (Xu *et al.*, 2020). There is a diversity of miRNA profiles across different types of diseases related to chronic hepatitis B. miR-145 and miR-199b exhibit decreased levels in mixed nodular cirrhosis with low serum AFP, while miR-224 decreases in early small HCC with nodules. miR-200c and miR-203 are more abundant in benign tumor cells, whereas miR-10b, miR-21, miR-26a, miR-122, miR-192, miR-222, miR-223, miR-801 are more prevalent in HCC and the expression patterns of these miRNAs vary with disease progression (Ladeiro *et al.*, 2008). miR-132 primarily decrease cell proliferation by blocking the Akt signaling pathway. HBx induces methylation in the promoter region of miR-132, reducing its inhibitory effect on cell proliferation and thereby manifesting tumor characteristics. HBV, either directly or indirectly through HBx, acts on the promoter of growth factor 5-inhibiting gene of miR-331–3p, enhancing its role in promoting cell proliferation, thus exhibiting tumorigenic traits (Cao *et al.*, 2015). The HBx protein can also indirectly exert its oncogenic effects through miRNAs, such as through its interaction with miR-101 targeting the 3' UTR of DNA methyltransferase 3A, a gene with a silencing effect on gene expression. This interaction results in reduced mRNA and protein levels of DNA methyltransferase 3A, decreasing the inhibitory effect on the HBx protein and thereby contributing to carcinogenicity or tumorigenicity. MiR-148a targets the protein kinase mTOR in the AKT/ERK/FOXO4/ATF5 signaling pathway, where the main physiological role of mTOR's is to promote cell proliferation, migration, and invasion (Zhang *et al.*, 2019). HBx mainly reduces the expression levels of miR-148a by interacting with P53 at the miR-148a gene promoter, thereby a weakening its oncogenic

effects. The negative regulation of HBXIP protein on HBx inhibits viral replication. MiR-501 counteracts the inhibitory effect of HBXIP, increasing HBV replication and HBsAg expression, thereby exhibiting tumorigenic characteristics. HBx induces high methylation in the promoter of miR-205, leading to reduced tumor-suppressive effects of miR-205. MiR-21 targets the pro-apoptotic protein PDCD4, affecting cell proliferation, and HBx enhances the effect of miR-21 to promote cell proliferation. MiR-181a primarily functions by acting on the transcription factor E2F5c, and HBx promotes cell proliferation and tumor formation by affecting the miR-181a promoter (Coulouarn *et al.*, 2009). Research has revealed that miR-129–2 exhibits enhanced methylation, leading to the oncogenic expression of SOX4, thereby exerting inhibitory effects in the development of HCC. The frequency and intensity of miR-129–2 methylation in tumor tissues are increased compared to non-tumor tissues (Chen *et al.*, 2013). The let-7 family include 12 tumor-suppressive miRNAs which are highly expressed in liver cells. They mainly exert their tumor-inhibitory effects by targeting multiple proliferative pathways such as STAT3, Ras, and c-MYC proliferation factors (Johnson *et al.*, 2005). Let-7a primarily targets and modulates the JAK/STAT signaling pathway, inhibiting cell proliferation through the downregulation of STAT3 (Xu *et al.*, 2021). HBx can downregulate the expression levels of let-7a, leading to the suppressed expression of many let-7a miRNAs in various tumor cells (Roush and Slack, 2008). miR-15 family represents the earliest-discovered tumor-suppressive miRNAs, and in HCC, six miRNAs within this family exhibit downregulated expression levels: miR-15a, miR-15b, miR-16–1, miR-16–2, miR-195, and miR-497. The potential influencing factors include the high expression of HBx and cell cycle-regulatory proteins such as cyclin D1. The realization of its tumorigenic characteristics may also involve the downregulation of anti-apoptotic Bcl-2 (Ahmed Youness *et al.*, 2020).

Hepatocellular Carcinoma Up-Regulated Long Non-Coding RNA (HULC) and HBV

The HULC is located on chromosome 6p24.3 and transcribes an approximately 500 nt RNA. It is a long non-coding RNA (lncRNA) localized in the cytoplasm, exhibiting significantly upregulated expression in hepatocellular carcinoma (HCC) and other tumors (Hämmerle *et al.*, 2013). Liu *et al.* studied involving 1300 cases of HBV-positive HCC patients, 1344 HBV carriers, and 1344 individuals with natural HBV clearance, found a potential association between single nucleotide polymorphisms (SNPs) in HULC and the risk of HCC (Liu *et al.*, 2016c). Specifically, the SNP rs7763881 in HULC showed a significant correlation with susceptibility to HCC in HBV carriers, and the variant allele C of rs7763881 was associated with a reduced risk of HCC, aligning with the biological function of HULC. According to the International HapMap Project, HULC has 5 SNPs, all of which are in a high linkage disequilibrium (LD) state (Scheet and Stephens, 2008). Notably, rs7763881 and rs1328867 are in complete LD, with the latter located in the promoter region of HULC. The c-myc gene plays a crucial role in regulating cell growth, differentiation, and apoptosis (Lin *et al.*, 2010). According to data from the University of California, Santa Cruz (UCSC), and transcription factor prediction software, the wild-type allele T of rs1328867 is predicted to bind to multiple transcription factors, including the c-myc gene, whereas the variant allele C is not expected to do so. Du *et al.* found that HBx upregulates the expression of HULC RNA in immortalized human normal liver cells and liver cancer cells (Du *et al.*, 2012). Examination of 33 HCC tissues revealed a negative correlation between HULC RNA levels and the tumor suppressor gene p18 RNA expression. Fluorescent reporter gene assays and chromatin immunoprecipitation assays demonstrated that HBx activates the HULC promoter by binding to the cyclic adenylic acid (cAMP) response element-binding protein. The upregulation of HULC by HBx inhibits the expression of the tumor suppressor gene p18, thereby promoting the proliferation of liver cancer cells. Ruan *et al.* utilized RNA immunoprecipitation to investigate the interaction between Hepatitis B Virus X-interacting protein (HBXIP) and two long non-coding RNAs HULC and hepatocellular carcinoma up-regulated EZH2-associated long non-coding RNA (HEIH), associated with the upregulation of EZH2 in liver cancer cells (Ruan *et al.*, 2018). The results demonstrated a positive interaction between HBXIP and both HULC and HEIH. Additionally, the expression level of HBXIP was found to be higher in HBV-positive HCC compared to HBV-negative HCC patients (Ruan *et al.*, 2018). Wang *et al.* further suggested that HBXIP might contribute to tumor development by enhancing angiogenesis in HCC (Wang *et al.*, 2012). Therefore, the elevated expression of HULC and HEIH may potentially promote the expression of HBXIP, thereby facilitating HBV proliferation and the occurrence of HBV-related diseases.

The APOBEC3 Gene Family and HBV

The APOBEC3 gene family includes seven types of cytidine deaminases (Salter *et al.*, 2016). APOBEC3's potential impact on HBV involves negative-strand C-U mutations, leading to a high mutational load of multiple G-A substitutions in the sense strand of HBV (Simmonds and Ansari, 2021). The endogenous cytidine deaminase activity of APOBEC3 affects DNA repair and integrity (Chen *et al.*, 2012). APOBEC3 mediates HBx mutations, particularly C-terminal truncating mutations leading to clonal expansion and proliferative advantage (Barnes and Lindahl, 2004). APOBEC3B, APOBEC3C, APOBEC3F, and APOBEC3G can affect the antisense strand of HBV DNA, while APOBEC3B, APOBEC3F, and APOBEC3G can also impact the sense strand of HBV DNA. APOBEC3B, APOBEC3D, APOBEC3F, and APOBEC3H are overexpressed in HCC tumor tissues, with APOBEC3G, APOBEC3F, and APOBEC3H mainly exhibiting antagonistic effects against HBV (He *et al.*, 2019). APOBEC3G and APOBEC3F are risk factors associated with the development and survival of HCC, while APOBEC3C and APOBEC3H play positive roles in HCC invasion and prognosis (Yang *et al.*, 2015). Elevated APOBEC3F in HCC tumor tissues promotes vascular invasion, intrahepatic metastasis, and increased alpha-fetoprotein levels, while APOBEC3H play a protective role in HBV infection (Xu *et al.*, 2007). APOBEC3B is a key molecular inducer of gene mutations in human HCC development, with its overexpression being associated with various tumors.

Persistent chronic HBV infection, facilitated by the high mutational load of G-A induced by the APOBEC3 family, can also impact the expression of genes in the Pre-C region, particularly the G1896A mutation. This mutation leads to a reduction in the synthesis of HBeAg and HBcAg, resulting in HBeAg serum conversion and immune escape (Yang *et al.*, 2015). The APOBEC3 family similarly influences the expression of HBsAg, especially through the mutation of glycine to arginine at amino acid position 145 (G145R) (Evans *et al.*, 2008). This mutation is associated with vaccine failure in hepatitis B immunization (Lazarevic *et al.*, 2019), leading to asymptomatic HBV infection and contributes to the persistence of HBV infection. This, in turn, further promotes the development of HBV-related diseases, including HCC.

HBV Involve in Activating Oncogenic Pathways

The oncogenicity of HBV is closely associated with activation of multiple tumor-related signaling pathways in its host cells. The mutations and integration of HBV described above result in abnormal expression of several molecules in host cells, many of which are located at key positions in carcinogenic signaling pathways.

Wnt/β-catenin pathway

An abnormal activation of the Wnt/β-catenin signaling pathway has been observed in approximately 66% of patients with HCC (Totoki *et al.*, 2014). Different molecular entities, such as the protein constituents of HBV and HCV are capable of initiating the Wnt/β-catenin signaling cascade in HCC cells (Aicher *et al.*, 2018; Daud *et al.*, 2017). The regulation of WNT ligand or FZD receptor expression could potentially explain the activation of the Wnt/β-catenin pathway in the absence of CTNNB1, APC, or Axin gene mutations. HBx competitively binds to the APC protein, displacing the degradation complex of β-catenin, resulting in the nuclear accumulation of β-catenin and the activation of Wnt signaling pathways, thus promoting transformation of cells into a malignant phenotype (Hsieh *et al.*, 2011). In mice, β-catenin contributes to the development of HCC through its interaction with other oncogenic pathways, including insulin/IGF-1/IRS-1/MAPK, H-RAS, MET, and AKT (Tan *et al.*, 2005; Stauffer *et al.*, 2011). It has been observed that HBV maintains the activation of β-catenin via multiple pathways. This activation is closely linked to upregulation of downstream elements, notably cyclin D1 and c-myc. Additionally, the activation of β-catenin enables it to engage with various transcription factors such as TCF and HIF-1α. This interaction plays a significant role in regulating the expression of specific target genes, consequently contributing to the development of the disease (Monga, 2015).

PI3K/AKT pathway

The PI3K/Akt signaling pathway plays an important role in various crucial physiological activity, including cell proliferation, apoptosis, differentiation, and metabolism, by influencing the activation of downstream effector molecules. The infection of hepatocytes by HBV is related to the upregulation of PI3K/AKT (Chin *et al.*, 2010). PTEN is a tumor suppressor that blocks the PI3K/Akt pathway, whereas HBx modulates liver cell proliferation and promote HBV-related cancers by inhibiting PTEN and activating Akt (Chung *et al.*, 2003; Kim *et al.*, 2021). Akt signaling pathway also plays a role in regulating the transcription and replication of HBV (Sun *et al.*, 2018). In a transgenic mouse model, the HBx mutant K130M/V131I also promotes the formation of hepatocellular carcinoma by activating Akt signaling (Chiu *et al.*, 2019).

Oxidative stress pathways

Mitochondria are the primary site for the generation of adenosine triphosphate (ATP) through electron transport, with ATP being the main source of cellular energy and closely associated with the production of reactive oxygen species (ROS). Recent studies have found an increase in ROS in cells infected with the HBV virus, and this increase is closely linked to lipid peroxidation and the progression of HCC, particularly in the context of mitochondrial-related HBX inducing oxidative stress in liver cells, leading to the production of large amounts of ROS (Lin *et al.*, 2018). High levels of ROS typically cause DNA oxidative damage and the formation of 8-hydroxy-2'-deoxyguanosine (8-OHDG), a marker of oxidative stress, while cells protect their genome through nucleotide pool sanitizing enzymes such as NUDT1, MTH2 (NUDT15), MTH3 (NUDT18), and NUDT5 (Lin *et al.*, 2018). Further research has found that HBX can significantly increase levels of 8-OxODG at both mRNA and protein levels in liver cells, reduce the expression of MTH1 and MTH2 to intensify oxidative stress, and accelerate the progression of hepatocellular carcinoma (Qing *et al.*, 2019). ROS have been demonstrated to play a direct promotive role in liver fibrosis and cancer induced by HBV (Xie *et al.*, 2020; Lee *et al.*, 2004). Thyroid hormones can mitigate liver cell damage induced by HBX. Treating HBX transgenic mice with thyroid hormones (TH) was shown to alleviate DNA damage caused by reactive oxygen species (ROS) (Chi *et al.*, 2017).

MAPK pathway

The MAPK signaling pathway is a protein kinase system composed of serine/threonine protein kinases, including the sub-pathways of ERK1/2, JNKs and p38MAPK. The activation of the MAPK signaling pathway plays a significant role in the development of HBV-related HCC. Following HBV infection of host hepatocytes, it can induce the upregulation of cell cycle proteins, matrix metalloproteinases, suppression of inflammatory factor expression, and inhibition of HBV replication through the MAPK signaling pathway. It has identified a novel long noncoding RNA, lncIHS, regulated by HBx which promotes hepatocellular carcinoma progression by enhancing cell migration, invasion, and proliferation through the ERK signaling pathways (Chen *et al.*, 2019b). HU *et al.* co-cultured JNKs inhibitor SP600125 with hepatocellular carcinoma cells carrying the HBV virus and observed

downregulation in the expression of JNKs, c-Jun, and autophagy-related proteins (Hu *et al.*, 2019b). This indicates that the JNKs cascade pathway can contribute to the carcinogenic process in HBV-related hepatocellular carcinoma by promoting autophagy in liver cancer cells. Yang *et al.* observed HepG2-NTCP liver cancer cells in the early stages of HBV infection using immunofluorescence and found a significant increase in the expression of p38MAPK, phosphorylated p38MAPK, and STAT3, along with a notable increase in HBV replication and liver cancer cell proliferation (Yang *et al.*, 2019). In the later stages of HBV infection, p38MAPK rapidly recruits the tyrosine phosphatase SHP-1 upon binding with the cell differentiation regulator HoxA10, which promotes the dephosphorylation of p38MAPK/STAT3, resulting in reduction in HBV replication and liver cancer cell proliferation (Yang *et al.*, 2019). This indicates HoxA10 plays an important role in regulating feedback loops that contribute to the persistence of HBV infections. This may provide potential strategies for controlling HBV infection and associated cancers through the development of novel therapeutic agents. Although each sub-pathway within the MAPK family can regulate the onset and progression of HBV-related HCC from different aspects, the functions of these sub-pathways are not entirely independent. They interact and regulate each other, forming a complex network of signaling pathways that influence the course of HBV-related HCC (Panteva *et al.*, 2003).

HBV and Metabolism

To support the rapid growth of malignant cells and adapt to hypoxic conditions, tumor tissues preferentially utilize glycolysis for energy production, even in the presence of oxygen. Glucose is more readily metabolized to lactate in tumor tissues compared to normal tissues. This energy metabolism mode, discovered in 1920, is known as the Warburg effect (Potter *et al.*, 2016). HBV infection and related somatic mutations are significant contributors to the Warburg effect. In HBV-associated HCC, the predominant pattern of mitochondrial DNA (mtDNA) single nucleotide variations is C>T, characteristic of APOBEC-induced mutations (Liu *et al.*, 2021b). These mutations primarily occur in the D-loop region of mtDNA, promoting proliferation, invasion, and metastasis of HCC cells (Yin *et al.*, 2019). The mitochondrial genome, particularly the genes involved in oxidative phosphorylation, are key targets of HBV integration (Giosa *et al.*, 2023). HBx protein can also upregulate glucokinase activity via phosphorylation of NF-κB and activation of the PI3K pathway, thus promoting aerobic glycolysis (Chen *et al.*, 2022). In addition to the Warburg effect, HCC cells enhance other energy metabolism modes during evolution. For instance, the K130M/V131I mutation in HBx promotes HCC adaptation to hypoxic environments by altering arachidonic acid metabolism (Chiu *et al.*, 2019). In patients with HBV-infected HCC, significant changes occur in lipid metabolism-related genes in HCC tissues. The number of abnormally expressed lipid metabolism genes is closely associated with the prognosis of HCC surgery, abnormalities in lipid metabolism leading to altered levels of angiopoietin-like protein 6 (ANGPTL6) can be detected in serum samples and serve as markers for early screening (Zhou *et al.*, 2023), indicating that the mechanisms by which HBV promotes HCC are also related to altered lipid metabolism patterns.

Treatment

Chronic hepatitis B (CHB) can progress to liver fibrosis, cirrhosis, and even hepatocellular carcinoma. Antiviral therapy is an essential measure to control the progression of CHB to cirrhosis and hepatocellular carcinoma (Lee and Banini, 2019). Nucleotide analogs are recommended as first-line drugs for the treatment of CHB, according to CHB management guidelines. They competitively inhibit the activity of HBV DNA polymerase, suppress HBV DNA replication, exhibit potent antiviral effects, and have good safety profiles (Fung *et al.*, 2011). Lamivudine (Lam) and Entecavir (Ente) are nucleoside/nucleotide analogs with demonstrated efficacy in the clinical treatment of chronic hepatitis B (CHB) (Lee *et al.*, 2014). They can be utilized for clinical antiviral therapy against primary liver cancer caused by hepatitis B virus (HBV).

Human T-cell Leukemia Virus (HTLV-1 and HTLV-2)

Human T-cell leukemia virus type 1 (HTLV-1), the inaugural human retrovirus identified, is widespread across various global regions, often overlooked in healthcare settings and by public health authorities. The identification of the initial human retrovirus unfolded independently in Japan and the United States. In 1980, Poiesz *et al.* pinpointed human T-cell leukemia virus (HTLV) in a T-cell line derived from a patient with cutaneous T-cell lymphoma (Poiesz *et al.*, 1980). Simultaneously, in 1982, Yoshida *et al.* discovered adult T-cell leukemia virus (ATLV) (Yoshida *et al.*, 1982). Subsequently, HTLV and ATLV were found to be identical at the sequence level and were designated as HTLV type 1 (HTLV-1) (Gallo, 2005). Given its usual asymptomatic phase early in infection and the subsequent manifestation of disease later in life, silent transmission occurs, linked to activities like sexual relations, breastfeeding, and blood transfusions. Active transmission is evident in numerous regions, including parts of Africa, South and Central America, the Caribbean, Asia, and Melanesia. HTLV-1 induces severe human diseases, including adult T-cell leukemia/lymphoma (ATL) and a debilitating neurological condition (HTLV-associated myelopathy/tropical spastic paraparesis [HAM/TSP]), along with other health issues such as uveitis, rheumatic syndromes, and heightened susceptibility to helminthic and bacterial infections, among others.

Following the revelation of HTLV-1, a second human retrovirus, HTLV-2, was delineated. Endemic infection has been established in Central and West Africa, among native Amerindian populations in North, Central, and South America, and within cohorts of intravenous drug users/abusers (IVDAs) in the United States and Europe and estimated to have 3–5 million cases globally (Feuer and Green, 2005).

Splenic tissue from a patient with hairy cell leukemia was the initial source of HTLV-2 identification, and it shares a connection with HTLV-1 (Kannian and Green, 2010). HTLV-2 infection closely resembles to that of HTLV-1 infection. Both HTLV-1 and HTLV-2 has the capability to infect and transform T lymphocytes in culture (Kannian *et al.*, 2012). Although the precise impact of the virus on human disease is not yet fully understood, mounting evidence suggests a potential association with neurological disorders and possibly rare lymphoproliferative disorders. The challenge arises from the fact that HTLV-1 and -2 share approximately 70% sequence homology (Manns and Blattner, 1991), leading to serological cross-reactions that complicate the identification of HTLV-2-infected individuals (Goncalves *et al.*, 2010). HTLV-2 has been found in a limited number of patients exhibiting spastic myelopathy and varying degrees of ataxia (Araujo, 2020). Notably, there is at least one case where a patient presented with a chronic progressive neurological disease that clinically resembled HAM/TSP, indicating a potential association between HTLV-2 infection and the development of neurological disorders.

HTLV-1 is categorized into six reported subtypes (subtypes A to F). Numerous studies have investigated HTLV-1 subtyping but indicate a limited role in the virus's epidemiological status. The overwhelming majority of infections stem from the cosmopolitan subtype A, with no reported influence of subtypes on the pathogenic potential of HTLV-1 (Ehrlich *et al.*, 1992).

Previous research aimed to understand the process by which HTLV-1 induces cancer. It has been observed that HTLV-1, in contrast to other rapidly transforming retroviruses, does not prompt fast tumor development or elevate the expression of cellular proto-oncogenes. Generally, viral infections can instigate and support tumorigenesis through various means: inducing chronic inflammation in the host, suppressing the host immune system, causing insertional mutations in the host genome, and activating virally carried oncogenes that facilitate cellular transformation (Chen *et al.*, 2008; Guo *et al.*, 2010; Yang *et al.*, 2013).

Studies have indicated that HTLV-1-induced oncogenesis may involve multiple mechanisms (Ohshima and Bartsch, 1994; Huebner and Todaro, 1969). Firstly, prolonged and persistent HTLV-1 infection leads to chronic inflammation in the host (Zhang *et al.*, 2017) which induces phagocytes to release reactive oxygen species at the inflammatory site, interacting with nitrogen radicals, causing damage to the cell membrane, DNA, and proteins. This alteration in gene expression profiles and enzymatic activities results in carcinogenesis and heightened neoplasia (Ohshima and Bartsch, 1994). Secondly, HTLV-1 infection can facilitate the insertion of efficient oncogenes into the host genome, thereby reducing the expression of tumor suppressor genes or directly stimulating host cell mitosis. Thirdly, HTLV-1 infection can hinder host immune function, impair immune surveillance, and consequently allow pre-cancerous cells to evade host immunity (Huebner and Todaro, 1969). However, new insights into the specific mechanisms through which HTLV-1 induces tumorigenesis are anticipated to emerge in the future through the application of novel approaches.

HTLV-2 have been categorized into four main subtypes: HTLV-2A/B/C/D (Eiraku *et al.*, 1996). Although instances of HTLV-2 infection leading to sub-acute neurological syndromes, such as neuropathies and paraparesis, are rare, they do occur (Verdonck *et al.*, 2007; Roucoux and Murphy, 2004).

Two additional members of the HTLV family, human HTLV-3 and HTLV-4, were identified more recently. In 2005, Gessain's group and others reported the discovery of HTLV-3 in two asymptomatic individuals in South Cameroon. Concurrently, a fourth type, HTLV-4, was found in the same geographical area. Molecular biology investigations revealed that the HTLV-4 lineage predates the ancestors of HTLV-1, HTLV-2, and HTLV-3 (Switzer *et al.*, 2009). Despite uncovering distinguishing characteristics of HTLV-3 and HTLV-4, the pathogenic potential of these human retroviruses remains undetermined.

It is noteworthy that the original designation for the human immunodeficiency virus (HIV), isolated by Gallo's team in 1984, was HTLV-3 (Gallo *et al.*, 1984), but this nomenclature has fallen out of use. It was collectively established that HIV was responsible for the new epidemic known as AIDS (Gallo, 2002b). Similar risk factors, such as blood exposure, sexual contact, and maternal transmission, were identified for both HTLV-1 and HIV-1 infections. Both viruses target immune system cells, particularly CD4 + T-cells, causing abnormal growth (HTLV-1) or cell death (HIV-1). Additionally, they encode regulatory proteins essential for viral replication, such as TAX and Rex for HTLV-1, and Tat and Rev for HIV-1 (Gallo, 2002a; Willems *et al.*, 2017). Despite sharing common transmission routes, HTLV-1 primarily leads to ATL, while HIV-1 ultimately results in the depletion of the human immune system.

Individuals with human immunodeficiency virus (HIV-1) face an elevated risk of developing various cancers, including Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), cervical cancer, and other malignancies associated with chronic viral infections. Traditionally, this heightened susceptibility is attributed to HIV-1-induced immune suppression, characterized by the depletion of CD4 + T-helper cells, lymphopoiesis exhaustion, and lymphocyte dysfunction. Despite the long-term and successful use of antiretroviral therapy (ART) initiated early in the course of infection, oncological complications persist (Isaguliants *et al.*, 2021). This suggests direct involvement of HIV-1 and its antigens in carcinogenesis, exerting their effects even in the presence of a restored immune system at extremely low levels.

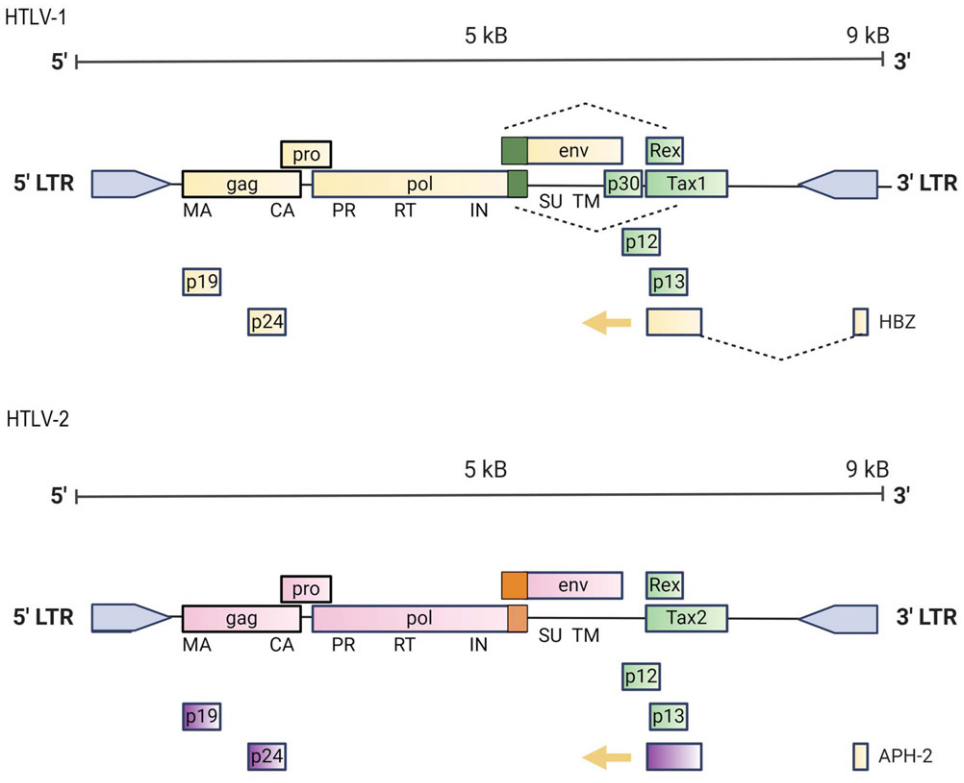
Experimental data supports the notion that HIV-1 virions and individual viral antigens can infiltrate various cells, including epithelial cells. This review focuses on the impact of five viral proteins—envelope protein gp120, accessory protein negative factor Nef, matrix protein p17, transactivator of transcription Tat, and reverse transcriptase RT. Gp120, Nef, p17, Tat, and RT induce oxidative stress, can be released from HIV-1-infected cells, and possess oncogenic properties (Hong *et al.*, 2012; Nyagol *et al.*, 2006; Tugizov *et al.*, 2013; Park *et al.*, 2014). All five proteins have the potential to affect bystander cells, leading to the propagation of existing malignant cells and the transformation of normal epithelial cells. This provides a foundation for the direct carcinogenic effects of HIV-1.

HTLV Genes and its Role in Tumorigenesis

HTLV-1 is causally associated with adult T-cell leukemia/lymphoma (ATL) (Proietti *et al.*, 2005). The genetic architecture and control mechanisms of HTLV-1 are more intricate compared to other leukemia viruses (**Fig. 3**) (Poiesz *et al.*, 1980). In addition to the structural genes (gag, pro, pol, and env) responsible for encoding characteristic virion proteins, the HTLV-1 genome harbors genes that encode nonstructural proteins, Tax and HBZ, crucial for regulating viral gene expression (Green and Chen, 1990). Despite significant advancements in comprehending the complex mechanism of ATL induced by HTLV-1, further exploration is essential to clarify the roles and regulation of the viral gene products, their interactions with one another, and their interplay with cellular factors.

Initial investigations have indicated that Tax-1 primarily localizes to the nucleus, specifically accumulating in the speckled structures of the nucleus (Semmes and Jeang, 1996; Nicot *et al.*, 1998). More recently, it has been noted that Tax-1 is also found in the cytoplasm (Burton *et al.*, 2000; Cheng *et al.*, 2001; Alefantis *et al.*, 2003), though the mechanisms governing its subcellular localization remain to be fully understood (Marziali *et al.*, 2017). The N-terminal segment of Tax-1 features a CREB-binding region (Yin *et al.*, 1995), essential for its interaction with proteins involved in cell cycle progression, transcription, and cell signaling regulation (Suzuki *et al.*, 1993; Goren *et al.*, 1995). Additionally, Tax-1 interacts with cellular factors like CAMP response element binding protein (CREB) and transcriptional co-activator CBP/p300 (Kashanchi and Brady, 2005). As a viral oncoprotein, Tax-1 plays a pivotal role in tumorigenesis, contributing to the pathogenesis of ATL by modulating various intracellular signaling pathways, including the IκB kinase (IKK)/NF-κB signaling pathway (Chen *et al.*, 2015), DNA damage repair pathway, and innate immune signaling pathways such as RIG-I/MDA5-dependent and TLR-independent pathways, TRIF-dependent TLR pathways, and the cGAS-STING pathway (Ishikawa and Barber, 2008; Ishikawa *et al.*, 2009).

Tumor cells are typically characterized by genetic and phenotypic instability, referred to as the mutant phenotype (Marriott and Semmes, 2005). Genomic injuries can occur due to internal (metabolic) and external (genotoxic stress) factors, as well as errors in DNA replication (Hollingworth and Grand, 2015). Normally, cellular repair mechanisms promptly correct these errors (Marriott



LTR: Long Terminal Repeat; gag: group-specific antigen; pro: protease; pol: polymerase; env: envelope; rex: regulator of expression; tax: transactivator; HBZ: HTLV basic leucine zipper; MA: matrix; CA:capsid; NC: nucleocapsid; PR: protease; RT: reverse transcriptase; IN: integrase; SU: surface; TM: transmembrane.

Fig. 3 Genomic organization of HTLV-1 and HTLV-2 (Zhang *et al.*, 2017).The genome of the HTLV-1 and 2 encodes three structural proteins—Gag, Pol, and Env—as well as intricate regulatory proteins like Tax. Tax not only triggers viral replication but also induces the expression of numerous cellular genes. In vivo, the expression of these viral proteins is curtailed by the activity of cytotoxic T lymphocytes (CTL). The HTLV-1 basic Zip factor (HBZ), generated by a minus-strand mRNA, likely contributes to viral replication and T-cell proliferation, persistently expressed in most HTLV-1-infected cells and primary adult T-cell leukemia (ATL) cells, in contrast to Tax (created with Biorender.com).

and Semmes, 2005). However, if these repair pathways are not tightly coordinated, genomic lesions may progress into mutations during cell division and DNA replication, leading to genomic instability. HTLV-1-transformed cells are thought to exhibit genomic instability induced by Tax-1-mediated inhibition of cellular DNA repair pathways (Jeang *et al.*, 2004) and increased mutations in the cellular genome (Hollingworth and Grand, 2015). The random nature of these mutations suggests that this viral protein could directly and indirectly interfere with DNA damage repair pathways, including BER (base excision repair), NER (nucleotide excision repair), MMR (mismatch repair), NHEJ (non-homologous end joining), and HR (homologous recombination). Specifically, Tax-1 has been shown to suppress the NER pathway by transactivating PCNA (proliferating cell nuclear antigen), a cofactor for DNA polymerase δ crucial in DNA replication and repair (Kao and Marriott, 1999; Cannon *et al.*, 1999). Additionally, through the inactivation of p53, Tax-1 can impede the function of the tumor suppressor (Pise-Masison *et al.*, 2000). Tax-1 exhibits a dose-dependent dual effect on NER, with high levels inhibiting p53-dependent NER and low levels stimulating NER by increasing the transcriptional activity of p53 (Pise-Masison *et al.*, 2000).

Furthermore, Tax-1 can disrupt cell cycle progression, leading to aberrant proliferation of HTLV-1-infected T-cells (Marriott and Semmes, 2005). Persistent activation of NF-κB is critical in supporting T-cell survival and malignancy. Tax-1 directly targets the Beclin1-containing autophagy molecular complex to deregulate autophagy by stimulating the IKK complex, resulting in the persistent activation of NF-κB (Chen *et al.*, 2015; Sun and Ballard, 1999). Autophagy not only plays significant roles in preventing inflammation and viral infections but also suppresses tumorigenesis by maintaining chromosomal integrity (Klionsky and Emr, 2000). A previous report has demonstrated that Tax-1 induces the production and secretion of pro-inflammatory cytokines, leading to the activation of the IL-6/STAT3 pathway in HTLV-1-transformed T-cells (Kimura *et al.*, 2013). Chronic inflammation is believed to increase the risk of tumor occurrence in such cases.

In 2002, a novel open reading frame (ORF) was identified on the minus strand of HTLV-1, giving rise to a unique basic leucine zipper factor named HBZ (Gaudray *et al.*, 2002). HBZ plays crucial roles in overseeing genomic integrity, cell proliferation, apoptosis, autophagy, and immune evasion (Zhao, 2016). Its influence on cell growth involves the formation of heterodimers with host factors, such as CCAAT/enhancer binding protein-α (C/EBP α) and activating transcription factor 3 (ATF3) (Zhao *et al.*, 2013). C/EBP α, a usual inhibitor of cancer cell proliferation, has its suppressive effect counteracted by HBZ. This occurs through interactions that reduce C/EBP α's DNA binding capacity and promote cell proliferation (Hendricks-Taylor and Darlington, 1995). ATF3, a binding partner of HBZ, has dual functions in oncogenesis, both activating p53 signaling as a tumor suppressor and promoting cancer cell proliferation (Pise-Masison *et al.*, 2000). Intriguingly, HBZ interferes with ATF3's p53-enhancing function without hindering its cell proliferative role in ATL cells (Pise-Masison *et al.*, 2000). Two separate studies indicate that HBZ utilizes autocrine/paracrine pathways to boost ATL cell proliferation (Pise-Masison *et al.*, 2000; Sun and Ballard, 1999). It suppresses the canonical Wnt pathway while enhancing ATL cell proliferation and migration through increased expression of noncanonical Wnt5a. Additionally, HBZ upregulates the expression of brain-derived neurotropic factor (BDNF) and its receptor, tropomyosin receptor kinase B (TrkB), further promoting ATL cell proliferation. HBZ-induced double-strand breaks (DSBs) are dependent on HBZ-inducible microRNAs (miRNA) like miR17 and miR21, which target and suppress OBFC2A, a gene encoding hSSB2, a single-stranded DNA-binding protein preventing genomic instability (Ma *et al.*, 2016). Thus, HBZ disrupts host genomic integrity through the HBZ-miRNA-OBFC2A cascade.

Moreover, HBZ suppresses apoptosis and autophagy in HTLV-1 infected cells (Ma *et al.*, 2016). It significantly downregulates the pro-apoptotic gene Bim, which is under the control of the important transcription factor FoxO3a. By impairing the DNA-binding ability of FoxO3a and forming a ternary complex with FoxO3a and 14–3–3, HBZ sequesters the inactive, phosphorylated FoxO3a in the nucleus (Tanaka-Nakanishi *et al.*, 2014). This repression of Bim transactivation leads to the inhibition of apoptosis. Autophagy, a cellular digestion mechanism, is negatively impacted by HBZ, as it activates the mTOR pathway by inhibiting growth arrest and DNA damage-inducible protein 34 (GADD34), a stress-induced GADD family protein inhibiting the mTOR pathway (Ma *et al.*, 2016). Furthermore, autophagy and the mTOR pathway are inversely coupled, with mTOR activation caused by HBZ inhibiting autophagy. Notably, among HTLV-1 viral proteins, HBZ exhibits the lowest immunogenicity, with anti-HBZ antibodies being scarcely detectable in HTLV-1-infected individual. A recent study proposes that the weak binding strength of HBZ epitopes to CTLs and the low expression of HBZ protein may significantly impede the host's ability to mount a successful anti-HBZ CTL response (Ma *et al.*, 2016; Zhang *et al.*, 2017). The low immunogenicity of HBZ is suggested to aid infected cells in evading immunosurveillance, thereby contributing to HTLV-1-mediated oncogenesis.

Current Treatment and Therapies

HTLV-1 infection, an overlooked and lifelong ailment, currently lacks a cure or effective treatment. The prevention of infection-related cancers could significantly decrease the incidence of human cancers. To curb the spread of HTLV-1, the development of a safe and efficient vaccine is imperative. While HBZ may be a promising target for ATL treatment, the effectiveness of the recombinant vaccine virus expressing HBZ and HBZ peptide-based vaccine needs further evaluation in human ATL (Sugata *et al.*, 2015). A previous study suggested that recombinant proteins from the immunogenic sequences of gp46 of the viral envelope had a positive impact on inducing robust immune responses (Lynch and Kaumaya, 2006). However, antigenic peptides face limitations in immunogenicity (Frangione-Beebe *et al.*, 2000). Enhancing immune responses can be achieved by combining peptide antigens with polymer-based nanoparticles like Chitosan (CHT) and Trimethyl-Chitosan (TMC) as delivery adjuvants. It would be intriguing to explore whether recombinant proteins of gp46 could be more effective candidates for HTLV-1 vaccination (Amirnasr *et al.*, 2016).

Despite the emergence of new therapeutic options, ATL patient treatment remains challenging. Some promising agents for ATL are undergoing translational research, with several in clinical trials. Notably, the anti-CCR4 antibody Mogamulizumab has gained approval for refractory ATL (Ishida *et al.*, 2004). Additionally, CD30 serves as an activation marker for lymphocytes, and a CD30-directed antibody-drug conjugate, Brentuximab vedotin, is being evaluated in a global phase III trial for ATL chemotherapy (Castellino *et al.*, 2022). Cancer immunotherapy has seen rapid progress, with chimeric antigen receptor (CAR)-modified T-cells showing promise. CAR-T cells, modified to recognize tumor antigens, could be employed in ATL therapy. For instance, the potency of CD19 CAR-T cells has shown unprecedented success in treating acute lymphoblastic leukemia (ALL) and B cell malignancies (Ghorashian *et al.*, 2015; Maude *et al.*, 2015). While CAR-T holds potential for ATL therapy, further clinical trials are necessary. Lenalidomide, an immunomodulatory agent, is undergoing testing in a phase II trial for relapsed aggressive ATL (Tsukasaki and Tobinai, 2014). Ongoing ATL trials include new agents like forodesine, pralatrexate, and IL-2 fused with the diphtheria toxin targeting CD25. Inhibitors such as histone deacetylase inhibitors (panobinostat, romidepsin, depsipeptide) and the proteasome inhibitor bortezomib have garnered attention in ATL research, but further studies are required to assess their efficacy and prevent potential side effects (Tsukasaki and Tobinai, 2014; Mesnard *et al.*, 2015).

Human Papillomavirus

Human Papillomavirus (HPV) is a small double-stranded DNA virus with a genome approximately 8 kb in length belonging to the papovaviridae family. This virus exhibits a high predilection for infecting cutaneous and mucosal epithelial cells (Groves and Coleman, 2015). To date, over 150 genotypes of HPV have been identified, with those infecting the genital tract categorized based on their pathogenicity into low-risk HPV and high-risk HPV types.

High-risk HPV types, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82; additionally, HPV26, 53, and 66 are classified as probable high-risk types (Burd, 2003). Low-risk types include HPV6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108 (Muñoz *et al.*, 2003). Epidemiological studies have shown that cervical cancers induced by high-risk HPV16 and HPV18 account for approximately 70% of all HPV-positive cervical cancers, with HPV16 infections being predominant globally. Other carcinogenic types, in addition to HPV16 and HPV18, include HPV31, HPV33, HPV45, and HPV58 (Demarco *et al.*, 2020). Notably, the prevalence of HPV58 has distinct regional specificity; it is the third most common HPV type causing cervical cancer in Asia, following HPV16 (Arbyn *et al.*, 2018).

HPV Structure

Generally, all types of HPV genomes consist of 8 open reading frames (ORFs) transcribed from a single DNA strand (**Fig. 4**). These ORFs can be divided into three functional parts: the early (E) region, encoding proteins necessary for viral replication (E1-E7); the late (L) region, encoding structural proteins required for virus assembly (L1 and L2); and the long control region (LCR), also known as the upstream regulatory region (URR), which contains cis-elements essential for viral DNA replication and transcription (Yu *et al.*, 2022). Viral E proteins are transcribed from early promoters (such as P97 in HPV31), while L proteins are primarily transcribed from late promoters (like P742 in HPV31). E1 and E2 proteins of HPV primarily function to identify the replication origin, with E2 also responsible for regulating the transcription of viral genes (Bhattacharjee *et al.*, 2022). E4 is considered to be associated with the later stages of the viral life cycle, despite being named as an early protein. E5 may function in both early and late stages. E6 and E7 proteins, target several cell cycle inhibitory proteins (mainly Rb and p53) (Nelson and Mirabello, 2023). In the viral life cycle, E6 and E7 maintain the stability of the viral episome and simultaneously stimulate differentiated cells to re-enter the S phase (Nelson and Mirabello, 2023).

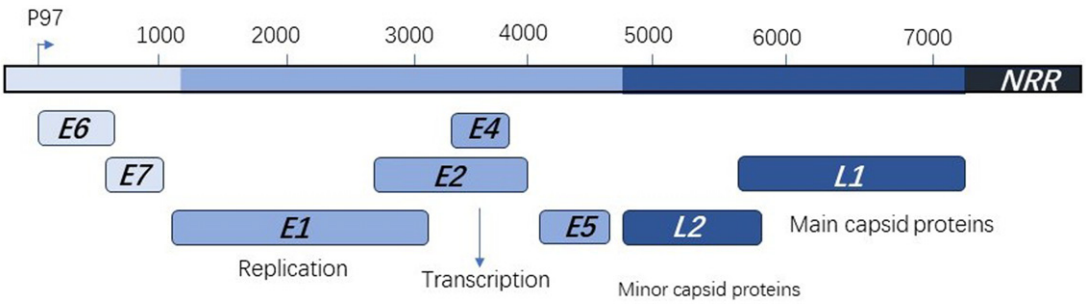


Fig. 4 The genome structure of HPV (Kim and Yang, 2006).The genome structure of HPV. Schematic representation of the HPV16 genome illustrates the positions of the early (E) and late genes (L1 and L2), as well as the long control region (LCR). The HPV genome encompasses eight thoroughly characterized proteins.

The Carcinogenic Mechanism of HPV

Despite the presence of the HPV genome in various cancers of diverse tissue origins, it has been most closely associated with cervical cancer. Cervical cancer ranks as the fourth most common cancer among women globally, following breast cancer, colorectal cancer, and lung cancer, with comparable mortality rates (Arbyn *et al.*, 2020). HPV is also strongly associated with head and neck squamous cell carcinoma (HNSCC), viral detection rate was 25% (Tanaka and Alawi, 2018). Similar to cervical cancer, the most common HPV subtype infecting HNSCC is HPV16, accounting for over 80% of HPV-positive HNSCC patients. Other HPV-associated cancers include breast cancer, anal cancer, vaginal cancer, penile cancer, and vulvar cancer (Gannon *et al.*, 2018). Then we will discuss the roles of different proteins of HPV towards our understanding of the mechanism of virus-induced carcinogenesis.

HPV E1, E2 and E4 proteins

When HPV infects host basal cells, E1 and E2 promote viral genome replication at a low copy number rate until the basal cells differentiate into suprabasal epithelial cells and then shed. At this point, the virus switches to a high copy replication rate (Burd, 2003). E1 is essential for HPV replication. As the E1 helicase is a crucial factor in separating DNA double strands during virus replication and is also the most conserved among the early-expressed HPV proteins, the utilization of HPV E1 protein, along with the potent adjuvant α-GalCer, to induce specific CD8 + T cell immune responses against HPV-E1 expressing cells, suggests a promising approach for therapeutic and prophylactic interventions against early HR-HPV infections and low-grade cervical intraepithelial lesions (Amador-Molina *et al.*, 2019). At the transcriptional level, E1 can bind to the upstream regulatory sequence of HPV, promoting the expression of the HPV E6 and E7 oncogenes (Kantang *et al.*, 2016). It has demonstrated that E1 activates specific cytotoxic T cell responses, which may initiate an early immune response against HPV infection. This response could potentially aid in clearing the virus before it progresses to carcinogenesis, thereby playing a role in the early stages of carcinogenesis (Ma *et al.*, 2018). Similarly essential for HPV replication is the E2 protein, which functions as a viral transcription regulator/activator and initiator of viral DNA replication. It is also necessary for recruiting and loading E1 at the viral replication origin. Although E1 is the primary viral DNA replication protein, E2 plays an important auxiliary role in assisting E1 to bind to the origin and assemble into a hexamer (Chojnacki and Melendy, 2018). HPV E4 has been proven to be a marker of HPV infection and disease progression. Studies show that E4 expression decreases as cervical intraepithelial neoplasias (CIN) progress. It's common in early stages (CINI), less in advanced stages (CINII/III), and nearly absent in cervical cancer. Research suggests that while E4 is more prevalent in CINII compared to CINIII, it's not a clinically significant biomarker for cervical lesions (Zummeren *et al.*, 2018, Stevenson *et al.*, 2018).

The E5 protein

E5 is a small transmembrane protein consisting of 83 amino acids, primarily localized on the intracellular membranes of the endoplasmic reticulum and Golgi apparatus (Venuti *et al.*, 2011). Recent studies have shown that E5 is important in cellular transformation and immune regulation, working in conjunction with E6 and E7 to drive the malignant progression of cells (de Freitas *et al.*, 2017). E5 promotes malignant progression by maintaining proliferative signaling in cells, helping cell escape death, increasing their invasive capabilities, and modulating the immune system. Research indicates that the E5 protein can form an activated complex with the Epidermal Growth Factor Receptor (EGFR), thereby promoting the proliferation of cancer cells and leading to a state of continuous cell proliferation (Wasson *et al.*, 2017). The E5 oncoprotein can also target and downregulate the signaling of the Keratinocyte Growth Factor Receptor/Fibroblast Growth Factor Receptor 2b (KGFR/FGFR2b), thereby reducing autophagy processes (Belleudi *et al.*, 2011). Simultaneously, E5 targets and inhibits cellular apoptosis by increasing the ubiquitination and proteasomal degradation of the pro-apoptotic protein Bax (Oh *et al.*, 2010). This plays a significant role in reducing cell death, which in turn promotes the accumulation of cells with abnormal DNA mutations, furthering malignant progression. E5 can also modulate the immune system. It interacts with Major Histocompatibility Complex class I (MHC class I), promoting the retention of MHC class I in the Golgi apparatus and inhibiting its transport to the cell surface. This results in a reduced ability of the complex to present viral antigens to T cells (Ashrafi *et al.*, 2006). Additionally, the E5 antigen is difficult for CD8 + T cells to recognize, which facilitates the immune evasion of HPV-transformed cells (Campo *et al.*, 2010).

HPV-encoded E6 and E7 proteins

After the discovery of the first high risk oncogenic HPV16, accumulated data indicated that the viral E6 and E7 proteins are key factors in maintaining the malignant phenotype of HPV-positive cancer cells (Durst *et al.*, 1983). Specifically, E6 and E7 are the only viral genes that are consistently retained and expressed in HPV-positive cancer cells (Schwarz *et al.*, 1985). The oncogenic drivers, E7 utilize the cellular ubiquitin-proteasome system (UPS) to degrade the retinoblastoma protein (pRB), thereby forcing the host cell into the S phase (Münger *et al.*, 1989). During this phase, cellular replication mechanisms and resources are abundant, such as nucleotide pools, facilitating viral replication. The E6 protein, by interacting with cellular E6-associated protein (E6AP) and the tumor suppressor protein p53, leads to the ubiquitination and proteasome degradation of p53 and anti-apoptosis, resulting in cell cycle arrest or unlimited proliferation (Bernard *et al.*, 2011). The E6 oncoprotein interacts with the conserved LxxLL motif of ubiquitin-protein ligase E3A (UBE3A), also known as ubiquitin-protein ligase E6-associated protein (E6-AP), serving as a bridging link between E6 and p53, targeting the degradation of p53 (Martinez-Zapien *et al.*, 2016). E6 can also bind to cellular PDZ proteins, leading to the disruption of cell polarity and signal transduction (Scheffner and Whitaker, 2003). Recent studies have

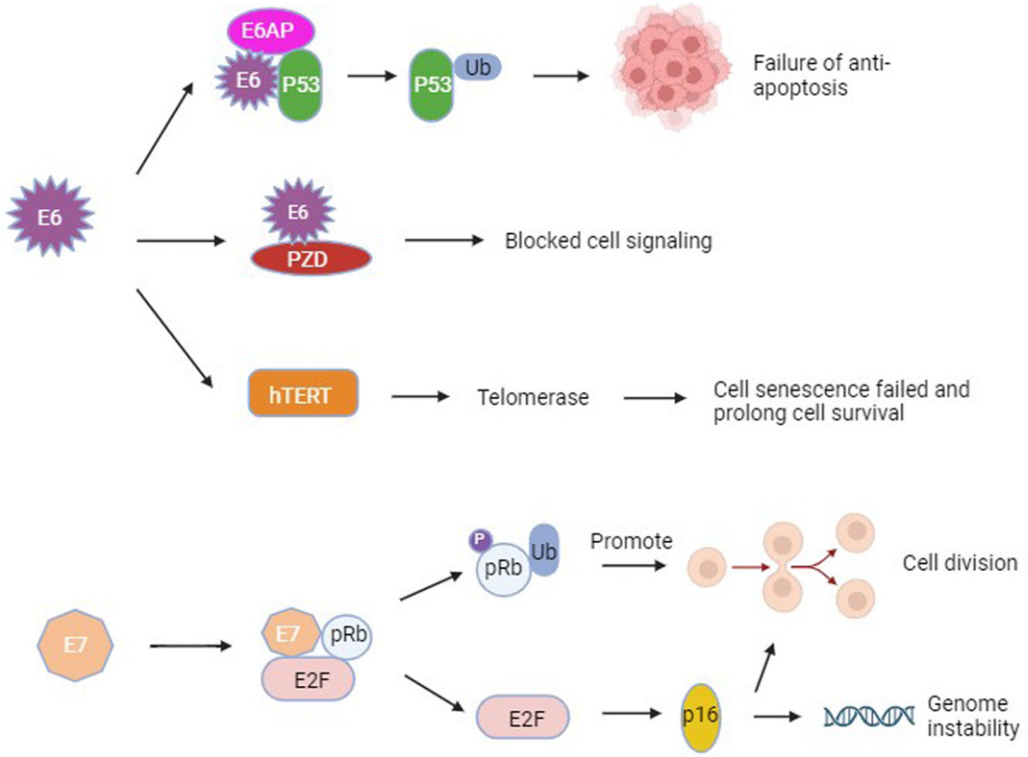


Fig. 5 Molecular mechanism of carcinogenesis by high-risk HPV E6 and E7 oncoproteins interacting with cellular proteins.Molecular mechanism of carcinogenesis by high-risk HPV E6 and E7 oncoproteins interacting with cellular proteins. Expression of the HPV E7 oncoprotein alone leads to the deregulation of cell genome instability by inactivating pRb (and other factors).

shown that E6 upregulates the protein complex nuclear factor kappa B (NF-κB), a nuclear factor that plays a significant role in various cellular functions. This upregulation can lead to the transcription of anti-apoptotic proteins such as cIAP-2, thereby preventing cell apoptosis (Philip and Shivakumar, 2013). In addition, the E6 oncoprotein can inhibit cell apoptosis by blocking the Fas/Fas ligand death-inducing pathway (Filippova *et al.*, 2007). The E6 protein can also activate the cellular telomerase (hTERT), leading to unlimited cell proliferation (Mantovani and Banks, 2001). E6 can also directly modulate the immune system by downregulating interferon regulatory factor 3 (IRF-3), a known transcription factor for interferon β (IFNβ), thereby reducing the immune response against HPV antigens (Shah *et al.*, 2015).

The E7 is the earliest discovered oncoprotein in HPV. As early as 1989, Dyson *et al*. observed that the E7 oncoprotein targets the pRB protein, specifically by inducing its ubiquitination through the cullin2 containing E3 ubiquitin ligase, subsequently leading to its degradation (**Fig. 5**). This results in the release of E2F transcription factors and dysregulation of cell proliferation (Dyson *et al.*, 1989). Similar to E6, E7 can also disrupt interferon signaling pathways, and it can bind to and inhibit Toll-like receptor 9 (TLR9). Additionally, E7 blocks the cyclic GMP-AMP synthase - stimulator of interferon genes (cGAS-STING) immune activation pathway, a key component of the innate immune system used for detecting cytoplasmic DNA (Songock *et al.*, 2017). E7 can directly inactivate the fundamental regulators of the G1 to S phase transition, namely the cyclin-dependent kinase inhibitors p21 and p27. The inactivation of these proteins, by maintaining the activity of cyclin-dependent kinase 2 (CDK2), leads to uncontrolled cell proliferation (Fischer *et al.*, 2017). E7 can also accelerate the turnover of claspin, a key positive regulator of the DNA damage signaling ATR-CHK1 pathway, allowing cells to continue proliferating even in the presence of DNA damage (Spardy *et al.*, 2009). E6 and E7 are recognized as the oncogenes most closely associated with cervical cancer. In synergy with E5, they promote the progression of cervical cancer through various cytokines, signaling pathways, and interactions with host cells.

The HPV L1, L2 and LCR

The HPV genome is packaged within the major capsid late protein L1 and the minor capsid protein L2. HPV L1 capsid protein is a marker of the complete life cycle of HPV as it reflects the state of virus replication in cells, and allows for prediction of the progression of cervical lesions through the detection of HPV L1 capsid protein expression (Hu *et al.*, 2019a). Zheng et at. conducted HPV DNA and HPV L1 screening on 596 patients with cervical lesions. They proposed that the combined detection of HPV DNA and L1 holds significant value for the diagnosis and prognostic risk assessment of cervical lesions, warranting clinical adoption (Wang *et al.*, 2015). Studies have shown that variations in the LCR are associated with persistent viral infections and the development of cervical cancer (Mosmann *et al.*, 2015). Notebly, the E2 protein has been demonstrated to be a transcriptional repressor, and mutations in the E2 binding sites within the LCR reduce the inhibitory effect mediated by p97, which is a highly

conserved AAA-ATPase protein involved in various cellular processes. P97 plays a crucial role in protein quality control, endoplasmic reticulum-associated degradation (ERAD), membrane fusion, and regulation of cell cycle. (Soeda *et al.*, 2006).

Treatment

The prophylactic HPV vaccines demonstrate remarkable efficacy in thwarting infection and the development of pre-invasive and invasive cervical, vulvovaginal, and anal diseases. These vaccines incorporate virus-like particles devoid of the viral genome, inducing the production of potent neutralizing antibodies. While they excel in preventing new infections, they do not accelerate the clearance of existing ones. Hence, vaccination initiatives focus on administering the vaccine to prepubertal girls and boys before their sexual debut, capitalizing on the highest efficacy in individuals who have not been exposed to HPV (Athanasiou *et al.*, 2020). Despite the established causal relationship between HPV and cervical cancer, the presence or absence of HPV currently does not influence treatment decisions. The focus remains primarily on anti-cancer strategies rather than anti-viral approaches, and as of now, there are still no FDA-approved drugs specifically targeting HPV (Bharti *et al.*, 2009). Currently oral hormonal medications used for anti-HPV drugs such as acyclovir, interleukin, ganciclovir and interferon. Among them, interferons (IFNs) are the sole antiviral agents authorized for treating benign HPV-related lesions (Cirelli and Tyring, 1994). Nonetheless, IFNα therapy exhibits restricted efficacy and is not advocated for routine clinical use in managing high-grade HPV-associated lesions. Additionally, certain traditional Chinese medicines demonstrate effective anti-HPV properties and have been utilized in China for the prevention and treatment of HPV-related cancers. Chaihu and Youdujing, traditional Chinese medicines, inhibit HPV-DNA expression in genital warts, while Paiteling eliminates or inhibits high-risk HPV infection (Xiao *et al.*, 2012; Li *et al.*, 2005; Guo-Qin, 2012). Xinfuning boosts NK cell activity to treat HPV infection in the vagina and combining it with Baofukang suppository is effective against high-risk HPV infection (Song *et al.*, 2011). Nevertheless, the current anti-HPV drugs are often costly, potentially causing liver and kidney damage, and may result in drug resistance with prolonged use. Hence, there is a critical need to develop new anti-HPV agents characterized by low toxicity and high efficacy.

Hepatitis C Virus

HCV infection is a worldwide health problem because of its incidence and pathogenicity. HCV belongs to the Hepacivirus genus within the Flaviviridae family, and its genome consists of single-stranded positive-sense RNA (Qureshi, 2007). The HCV genome is approximately 9.6 kb in length. Although there are non-coding regions at both ends of the genome, it contains only one open reading frame, which encodes a polyprotein (Thomas, 2013). The HCV genome coding region includes sequence for three structural proteins: the core protein (C), and the envelope proteins (E1, E2), along with six non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B) (Pirakitikulr *et al.*, 2016). The regions encoding the non-structural protein are associated with viral replication and protein expression and serve as the targets for direct-acting antiviral (DAA) drugs. Located in the 5' untranslated region is the Internal Ribosome Entry Site (IRES), which initiates the translation of viral proteins. It also acts as one of the Pathogen-Associated Molecular Patterns (PAMPs) that activate the host's innate immune system (Mogensen, 2009). The correct folding of this structure depends on the assistance of the 3' untranslated region of the HCV genome (Lindenbach and Rice, 2005). The 3' end of the HCV genome can bind with the HCV RNA polymerase, playing a crucial role in stabilizing the RNA replication template during replication. The core protein (Core) and envelope proteins (E1 and E2) are primarily involved in the virus's invasion and assembly (Bartenschlager *et al.*, 2013). The P7 protein and non-structural protein NS2 primarily participate in the assembly and release of viral particles (Jones *et al.*, 2007). NS4A, NS4B, and NS5A proteins mainly regulate the replication of the viral genome (Jones *et al.*, 2007). The NS3 and NS5B proteins are involved in viral replication, with protein NS5B encoding an RNA-dependent RNA polymerase (RdRp), which is essential for HCV replication and thus is a target for various drugs for therapeutic intervention.

HCV Core Protein and HCC

The intracellular localization of the HCV CORE protein in hepatocytes is a markedly characteristic signal for HCV infection, primarily existing in the cytoplasm and closely associated with lipid droplet formation (Tang *et al.*, 1995). It can also appear in mitochondria and the nucleus (Chou *et al.*, 2005). Therefore, pathways related to lipid droplet formation and mitochondrial function have become focal points of research. Hepatocyte steatosis is a significant characteristic of chronic HCV infection, with 50% to 80% of patients with chronic HCV infection exhibiting fatty changes in their liver cells (Ohata *et al.*, 2003). The prevalence of this condition in chronic HCV infection is 2.5 times higher than in other types of chronic hepatitis, including HBV (Decock *et al.*, 2007). Pre-existing liver cirrhosis is also an important risk factor for the development of HCC in patients with HCV, and it has been hypothesized that the carcinogenic effect of HCV involves chronic inflammation and sustained hepatic injury. However, HCC still occurs in a portion of HCV patients without liver cirrhosis, suggesting that HCV may directly contributes to HCC development (Vescovo *et al.*, 2016). Mice with constitutive expression of HCV core proteins exhibit a higher incidence of HCC, indicating that core proteins play an important role in the development of HCC (Tanaka *et al.*, 2008). Core proteins can also promote cell proliferation by interacting with cellular proteins (such as p53, p73, and pRb) or regulating cellular genes (like p21)

and intracellular signaling pathways (such as MAPK and Wnt/β-catenin pathways) (Inoue *et al.*, 2012; Plentz *et al.*, 2007). HCC core protein can transform the original tumor-suppressive response of TGF-β into promoting Epithelial-Mesenchymal Transition (EMT). This process, which involves the epigenetic modification of Secreted frizzled-related protein1 (SFRP1), contributes to increased invasiveness of HCC (Quan *et al.*, 2014). Additionally, the transcriptional activation of matrix metalloproteinases enhances the metastatic and invasive capabilities of infected hepatocytes (Feng *et al.*, 2011).

The pathogenesis associated with core protein induction of HCC also has genotypic characteristics. The overexpressed HCV 3a type core protein has a strong regulatory effect on Cyclooxygenase-2 (Cox-2) when compared to the HCV 1a type core protein (Jahan *et al.*, 2011). According to an analysis of clinical meta data on patients infected with genotyped HCV, the relative risk of developing HCC is 2.5 times higher in patients with certain genotypes compared to others (Dragani, 2010). This increased risk is also significantly higher in patients without liver cirrhosis, underscoring the genotype specificity of HCV. There are reports of observed sequence variations in core proteins extracted from cancerous and adjacent non-cancerous tissues of the same HCC patient. Therefore, variations in core proteins within the same genotype may have different pathogenic effects. Studies have shown that amino acid substitutions in the nuclear proteins of genotyped HCV (especially at positions 70–91) are associated with development of HCC (Khaliq *et al.*, 2011).

Unlike HBV, HCV RNA not integrate into the host genome, hence the mechanism of HCV-related HCC is mainly considered to be associated with oxidative stress (Ivanov *et al.*, 2013). Oxidative stress occurs when the balance between the production and clearance of ROS is disrupted. In the liver, ROS is primarily produced by mitochondria in hepatocytes, as well as by NADPH oxidase and myeloperoxidase reactions in Kupffer cells and inflammatory cells. Chronic oxidative stress can cause DNA damage, leading to accumulation of mutations. Additionally, ROS acts as a secondary messenger in intracellular signal transduction. Furthermore, the role of ROS is directly linked to damaging biomolecules and activating signaling pathways that affect gene expression related to cell survival and cancer progression. The oxidative stress caused by HCV is mainly attributed to expression of core proteins, which can lead to mitochondrial dysregulation (Ivanov *et al.*, 2013). This dysregulation inhibits the functionality of the electron transport complex I, resulting in the mitochondria producing a large amount of ROS (Ivanov *et al.*, 2013). HCV infection activates the ROS/JNK/Itch signaling pathway, which promotes poly-ubiquitylation of Vacuolar Protein Sorting 4 Homolog A (VPS4A), enhancing its interaction with charged multivesicular body protein 1B (CHMP1B) and ATPase activity, thereby facilitating the release of HCV particles (Deng *et al.*, 2022).

Chronic Inflammation and HCV

Inflammation also plays a significant role in the process of HCV infection (Atta *et al.*, 2012). The levels of cytokine expression in HCC tumors exhibited substantial alteration in cell morphology and survival. In HCC patients, there is a general upregulation of Th1 cytokines compared to healthy individuals. This leads to the elevation levels of proinflammatory cytokines such as IL-1β, IL-15, IL-18, TNF-α, TNF-αRs, TNF-αRI, TNF-αRII, and IL-6 (Huang *et al.*, 1999; Kakumu *et al.*, 1997; Chia *et al.*, 2002). Chronic inflammation leads to cycles of liver cell damage and regeneration, thereby increasing the likelihood of genetic mutations within the liver (Berzsenyi *et al.*, 2011). Emerging data also indicates that an inflammatory environment creates desirability condition for genetic mutations that can lead to malignancy. While typically an ineffective immune response has advantage for the host, both innate and adaptive, to HCV infection can result in a "vicious cycle." This cycle is associated more with the development of the host immune response rather than with the infection and viral replication itself (Farci *et al.*, 1996; Brillanti *et al.*, 1993). As a result of chronic inflammatory reactions triggered by viral infections, there is a release of free radicals, including reactive oxygen species and reactive nitrogen oxide (NO) species (Hussain *et al.*, 2003). NO support the persistence of viruses through its anti-apoptotic effects on HCC and could potentially induce viral mutations while exerting a selective suppressive impact on Th1 cells (Majano and Garcia-Monzon, 2003). NO also has a direct effect on liver cell survival, as it inhibits apoptosis by activating the NF-κB signaling pathway (Kato *et al.*, 2000). Consequently, the pathogenesis of HCC could serve as a model to examine the progression of disease from chronic inflammation to cancer, offering opportunities to develop new strategies that target the immune response and potentially alter the disease's trajectory.

Treatment and Management of HCV

Acute HCV infection often presents with nonspecific symptoms but can progress to jaundice or a temporary rise in amino-transferase levels, typically resolving within six months. The majority of individuals with acute HCV infection transition to chronic HCV infection, characterized by detectable HCV RNA persisting for over six months post-initial infection. Chronic HCV infection is considered untreatable without antiviral therapy. Given the effectiveness of direct-acting antivirals against HCV, guidelines from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommend that all patients with chronic HCV infection consult an HCV treatment provider for potential antiviral therapy, with the exception of those with a limited life expectancy unaffected by HCV eradication.

Delaying antiviral treatment may heighten the risk of hepatocellular carcinoma (HCC), underscoring the importance of treating all patients with chronic HCV infection before advanced fibrosis develops. The risk of HCC in individuals with chronic HCV infection is particularly elevated in those with advanced liver fibrosis and escalates significantly once cirrhosis sets in. Achieving sustained virologic response through interferon-based regimens has been associated with histologic improvement in liver fibrosis

and necrosis in a substantial percentage of affected patients, along with cirrhosis reversal in nearly half of cases. Likewise, significant reduction in liver stiffness, as measured by noninvasive methods like transient elastography, has been observed in patients with chronic HCV and advanced liver disease following sustained virologic response induced by direct-acting antivirals.

Chronic HCV infection can lead to elevated aminotransferase levels during cancer treatments, potentially delaying cancer management, and may expedite fibrosis progression. Thus, antiviral therapy should be considered for all HCV-infected cancer patients unless contraindications exist, such as a life expectancy under 12 months, known hypersensitivity to direct-acting antivirals, or anticipated major drug interactions with anticancer therapies (Torres *et al.*, 2017).

Despite numerous clinical trials aimed at developing an HCV vaccine, there is currently no effective vaccine available to counter the virus. This is primarily due to a range of challenges, including the virus's genetic diversity, the absence of suitable small animal models for immunocompetence testing, limited alternatives for HCV vaccine testing, the absence of a reliable tissue culture method for replicating HCV, and insufficient understanding of immune responses to HCV infection (Adugna, 2023).

Kaposi Sarcoma Associated Herpes Virus (KSHV)

Kaposi sarcoma-associated herpesvirus (KSHV) is a member of the γ-herpesvirinae subfamily, characterized by its large double-stranded DNA. KSHV possesses a double-stranded DNA genome with a size ranging from 165 to 170 kb (Renne *et al.*, 1996; Neipel *et al.*, 1998). The long unique region (LUR), approximately 138 to 140.5 kb in length and encompasses all KSHV ORFs, is flanked by terminal repeat (TR) sequences at both ends of the linear viral genome. Each TR, 801 bp in length, is notably GC-rich. The number of TRs varies among KSHV isolates, ranging from 16 to 75 (Wen and Damania, 2010), contributing to the diversity in genome sizes. The KSHV genome demonstrates a high degree of similarity to retroperitoneal fibromatosis-associated herpesvirus (RFHV) and rhesus monkey rhadinovirus (RRV) within the rhadinovirus subfamily of γ-herpesvirinae (Bruce *et al.*, 2013). RFHV appears to be more closely related to KSHV. While many KSHV ORFs are conserved in a- and b-herpesviruses, the virus contains a significant number of unique ORFs designated K1 to K15, not found in other herpesviruses. Additionally, KSHV incorporates several viral genes homologous to cellular genes pirated from the host genome. Numerous viral genes play roles in signal transduction (e.g., K1 and K15), cell cycle regulation (e.g., vCyclin and LANA-1), inhibition of programmed cell death (e.g., K1, vFLIP, and vBcl-2), and immune modulation (e.g., viral chemokine receptors, vIRFs, K3, and K5) (**Table 3**) (Lu *et al.*, 2004). Furthermore, alternative splicing, alternative transcriptional start sites, or internal ribosome entry sites (IRES) are employed in the expression of some KSHV genes (Lin *et al.*, 1999; Low *et al.*, 2001). Recently, 12 microRNAs were discovered in the KSHV genome, with 10 located in the non-coding region between K12/Kaposin and K13/Orf71/vFLIP, and two within the K12 ORF (Wen and Damania, 2010). All KSHV microRNAs are expressed during latency, with a subset upregulated during the lytic cycle (Ziegelbauer, 2011). These microRNAs have identified cellular and viral targets, contributing to KSHV pathogenesis (Murphy *et al.*, 2008; Samols *et al.*, 2007; Gottwein *et al.*, 2007; Skalsky *et al.*, 2007; Marshall *et al.*, 2007). In addition to microRNAs, KSHV produces a polyadenylated, exclusively nuclear non-coding RNA transcript known as PAN, 1077 bp in size, synthesized during the lytic cycle (Wen and Damania, 2010). PAN RNA has been shown to retain intron less RNA in the nucleus and hinder the assembly of an export-competent mRNP (Conrad *et al.*, 2006; Conrad and Steitz, 2005; Sun *et al.*, 1996; Zhong and Ganem, 1997).

KSHV has been linked to the development of a number of proliferative disorders like Kaposi sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman disease (MCD), and KSHV induced cytokine syndrome (KICS) (Karass *et al.*, 2017). PEL and MCD are primary disorder in B cell lineage while the KS is associated with proliferation of cells in the endothelial lineage.

Kaposi Sarcoma

In 1872, Dr. Moritz Kaposi, a distinguished Hungarian dermatologist, coined the term "idiopathic multiple pigmented sarcoma of the skin" to describe the rare classical form of Kaposi sarcoma (KS) (Sternbach and Varon, 1995; Kaposi, 1872). Although suspicions of an infectious cause for KS date back to the 1950s, it wasn't until the early 1980s, during the AIDS epidemic, that intensive investigations into the causative agent gained momentum. The notable increase in KS incidence among HIV-positive individuals, particularly in the homosexual and bisexual population, strongly indicated the involvement of an infectious agent in KS development.

In 1994, Chang and Moore employed representational difference analysis to scrutinize DNA fragments from KS biopsies, ultimately establishing an association between a novel human γ-herpesvirus and KS, which was subsequently named KSHV (Chang *et al.*, 1994). KS is identified as a highly vascular tumor with endothelial lymphatic origin, characterized histologically by spindle-shaped, poorly differentiated, and highly proliferative KSHV-infected cells. The tumor is also marked by erythrocyte extravasation, inflammatory cell infiltration (macrophages, lymphocytes, and plasma cells), and neoangiogenesis (Gessain and Duprez, 2005).

Clinically, KS manifests as dermatological lesions exhibiting red, brown, or purple pigmentation, present cutaneously, mucosally, or viscerally. KS is categorized into six overlapping clinicopathologic forms: patch, plaque, nodular, lymphadenopathic, infiltrative, and florid (Kyalwazi, 1981; Taylor *et al.*, 1971). It's noteworthy that over 95% of KS lesions contain KSHV viral DNA. Based on epidemiological and clinical criteria, KS is classified into four clinical subtypes: classic/sporadic, endemic/African, epidemic/AIDS-associated, and iatrogenic/post-transplant.

Table 3 KSHV genes and associated mechanisms of oncogenesis.

Open reading frame	*Oncoprotein*	*Function*	*References*
ORF73	LANA	• Viral genomic duplication and segregation of the DNA to the daughter cells. • Inhibition of apoptosis • KS cell proliferation	(Kedes *et al.*, 1997; Verma *et al.*, 2006)
ORF72	vCyclin	• Promotes cell cycle progression from G1 to S • KS cell prolferation	(Russo *et al.*, 1996; Ojala *et al.*, 1999)
ORF71	vFLIP	• Cell survival, proliferation and differentiation • Cytokine secretion • Oncogenic transformation • Apoptosis inhibition	(Thome *et al.*, 1997)
ORF74	vGPCR	• Viral replication and persistence • Activation of pro-inflammatory • Activation of angiogenic pathways	(Cesarman *et al.*, 1996; Smit *et al.*, 2002)
ORF16	vBCL2	• Inhibition of apoptosis • Inhibition of autophagy • Viral replication	(Sarid *et al.*, 1997)
ORFK2	vIL6	• Angiogenesis induction • Induction of hematopoiesis	(Nicholas *et al.*, 1997)
ORFK9	vIRF1	• Inhibition of apoptosis • Induction of tumorigenesis	(Zimring *et al.*, 1998)
ORFK10	vIRF3	• Deregulation of cellular response to viral infections • Apoptosis inhibition • Tumorigenesis	(Lubyova *et al.*, 2004)
ORFK1	K1	• Cellular signal transduction • Viral reactivation • Endothelial cell immortalization • Host immune recognition • Activation of tyrosine immunoreceptors	(Lee *et al.*, 1998)
ORFK15	K15	• Viral lytic replication • Inhibition of apoptosis • Activation pro-inflammatory • Angiogenic pathways	(Nicholas *et al.*, 1998)
ORF36	vPK	• Cell proliferation • Induction angiogenesis	(Park *et al.*, 2000)

The more aggressive variant of endemic KS, also known as the lymphadenopathic form, is frequently observed in children before puberty, exhibiting high fatality rates (Dutz and Stout, 1960). In contrast, AIDS-associated KS stands out as the most prevalent and aggressive subtype, characterized by extensive lymph node and visceral spreading compared to other KS variants (Biggar and Rabkin, 1996; Beral and Newton, 1998). An additional manifestation of KS, referred to as iatrogenic/post-transplant KS, is linked to immune suppression resulting from prolonged immunosuppressive therapy administered to prevent the rejection of solid allografts (Penn, 1988). Among those at higher risk for developing this type of KS, renal transplant patients are particularly noteworthy. Interestingly, the KSHV-infected endothelial cells or lymphocytes identified in KS lesions among these patients may originate from donor tissues (Pyakurel *et al.*, 2007). While reducing or discontinuing immunosuppressive therapy has proven effective in resolving iatrogenic KS, it also heightens the risk of allograft rejection (Bomholt *et al.*, 2019).

Primary Effusion Lymphoma

In addition to Kaposi sarcoma, primary effusion lymphoma (PEL), sometimes referred to as body cavity-based lymphoma (BCBL), is strongly linked to KSHV (Cesarman *et al.*, 1995). PEL represents a distinctive form of non-Hodgkin lymphoma (NHL) that is more prevalent among immunocompromised AIDS patients (Hashmi *et al.*, 2018). Unlike Kaposi sarcoma, PEL originates from clonally expanded malignant B cells and manifests as a lymphomatous effusion tumor confined to various body cavities such as the pericardium, pleura, and peritoneum. However, there have been reports of PEL presenting as a solid mass in lymph nodes and other organs (Arvanitakis *et al.*, 1996). PEL is characterized by its aggressive and rapidly progressing nature, often leading to high fatality. The average survival time for PEL patients is approximately 2–6 months (Komanduri *et al.*, 1996).

Histologically, PEL cells are larger than normal lymphocytes and erythrocytes, displaying features of both large cell immunoblastic lymphoma and anaplastic large cell lymphoma. These cells express CD45, activation-associated antigens, and clonal immunoglobulin rearrangements but typically lack B cell-associated antigens (Nador *et al.*, 1996).

Multicentric Castleman's Disease

The plasmablastic subtype of multicentric Castleman disease (MCD) exhibits a strong association with KSHV, while the hyaline variant of MCD does not share this association. MCD is characterized as a reactive lymphadenopathy, typically considered non-neoplastic due to the presence of polyclonal B-cell populations in the lesion. However, plasmablastic MCD has been reported to involve monoclonal B cell expansion as well (Radaszkiewicz *et al.*, 1989; Hall *et al.*, 1989). Plasmablastic MCD often displays aggressive and rapid progression, leading to a high fatality rate (Castillo *et al.*, 2015). Histologically, germinal center expansion and vascular endothelial proliferation occur within the affected lymph nodes of MCD (Saeed-Abdul-Rahman and Al-Amri, 2012).

Dysregulated levels of IL-6, potentially influenced in part by virally encoded IL-6 (vIL-6) (Parravicini *et al.*, 1997), may contribute to the clinico-pathophysiology of MCD. Like Kaposi sarcoma and primary effusion lymphoma, KSHV genomes are detectable in nearly all HIV-positive MCD cases and approximately 50% of HIV-negative MCD cases (Soulier *et al.*, 1995; Dupin *et al.*, 1999). Furthermore, KSHV was demonstrated to be associated with the plasmablastic variant of MCD (Carbone *et al.*, 2009).

Treatment Options for KS Induced Cancers

Treatment approaches for Kaposi's sarcoma (KS) depend on factors such as disease severity, KS subtype, and immune status. For mild and localized cases, options like topical alitretinoin, surgical excision, radiation therapy, and intralesional chemotherapy (e.g., Vinblastine) can address symptoms, although they do not prevent new lesions. Severe and aggressive KS often requires systemic chemotherapy with liposomal anthracyclines (Doxorubicin and daunorubicin) as the primary treatment, followed by paclitaxel if needed. Other options include vinorelbine, Interferon-α, and Interleukin-12, although their specificity in targeting the tumor-causing agent is limited. The mTOR inhibitor Rapamycin (Sirolimus) has shown high success against iatrogenic KS (Chaisuparat *et al.*, 2008).

In AIDS-related KS, highly active antiretroviral therapy (HAART) is recommended to reduce lesion extent and size, potentially lowering the incidence of new KS. Immune reconstitution likely contributes to these effects. Additionally, the tyrosine kinase inhibitor Imatinib and IL-12 show some activity against AIDS-KS (Koon *et al.*, 2014).

Patients with primary effusion lymphoma (PEL) face a grim prognosis, with a median survival of 2–3 months. Co-infected HIV patients may benefit from HAART, occasionally achieving complete remission. Conventional CHOP-like regimens do not significantly improve survival. Treatment options for HIV-negative PEL include liposomal anthracycline with or without Bortezomib, while Rapamycin has shown promise (Cesarman *et al.*, 2019). Radiation therapy is rarely employed but may be considered for patients' intolerant to other treatments.

Multicentric Castleman disease (MCD) treatment involves surgical excision, cytoreduction chemotherapy (CHOP or CVAD), radiation therapy, and immune modulators. Responses vary, and the preference for chemotherapy is based on severe systemic symptoms. Viral replication inhibitors (especially Ganciclovir), Interferon-α, and anti-IL-6 and anti-CD20 monoclonal antibodies are considered specific and promising options for MCD (Wen and Damania, 2010).

In conclusion, current treatments for KS, PEL, and MCD are sub-optimal. Advances in understanding KSHV biology and tumorigenesis are slowly translating into more effective clinical management. Antiviral agents and small molecules targeting specific signaling pathways of tumor cells are potential alternatives to conventional chemotherapy. Further case reports and randomized clinical trials are essential to standardize treatments for KSHV-associated malignancies.

Merkel Cell Polyomavirus

Merkel cell polyomavirus, abbreviated as MCV or MCPyV, belongs to the relatively small category of viruses that have been identified as causative agent of cancers in humans. It is among the eight recently discovered polyomaviruses affecting humans within the last fifteen years. MCV is a non-enveloped, double-stranded DNA virus belonging to the mammalian genus Orthopolyomavirus (Arora *et al.*, 2012). Discovered in 2008, MCV is found to be clonally integrated in approximately 80% of Merkel cell carcinoma (MCC) cases. MCV is commonly present in the skin's natural microbial community and only triggers cancer development in susceptible individuals once it undergoes specific mutations that render it unable to replicate.

Merkel cell carcinoma is a rare but aggressive type of skin cancer that carries a poor prognosis when it spreads. It originates from Merkel cells, which contain sparsely distributed mechanoreceptors located in the basal layer of the epidermis. Like other skin cancers, prolonged exposure to ultraviolet (UV) radiation increases the risk of Merkel cell carcinoma, as does older age, with a significant increase in risk for individuals aged 50 or older. Notably, a weakened immune system is strongly associated with an elevated risk of Merkel cell carcinoma. AIDS patients have a 13-fold higher risk, while organ transplant recipients have a 10-fold higher risk compared to the general population (Shaffer and Durand, 2018). This epidemiological pattern is reminiscent of cancers with a viral cause, such as Kaposi's sarcoma.

In the United States, around 2500 cases of Merkel cell carcinoma (MCC) are reported each year, surpassing the number of deaths caused by chronic myelogenous leukemia. Interestingly, there is a notable association between MCC and other cancers, including chronic lymphocytic leukemia, basal cell carcinoma, and squamous cell carcinoma, occurring at unexpectedly high frequencies. However, there is currently no strong evidence linking these secondary cancers to Merkel cell polyomavirus (MCV) infection, and reports differ regarding the presence of MCV in these non-MCC tumors.

MCPyV Genomic Organization

The MCPyV features a circular double-stranded DNA genome of approximately 5.4 kb (Spurgeon and Lambert, 2013), as depicted in **Fig. 6**. Like other polyomaviruses, existing evidence indicates that the MCPyV genome remains episomal throughout the infectious cycle (Krump and You, 2021; Liu *et al.*, 2016a,b). The viral genome is partitioned into early and late regions by a non-coding control region (NCCR), housing the viral origin of replication and bidirectional promoters responsible for early and late gene transcription (Harrison *et al.*, 2011). Within the early region, alternatively spliced tumor antigens—referred to as large tumor antigen (LT) and small tumor antigen (sT)—support replication, alongside the 57kT and an alternate LT open reading frame (ALTO) with less defined functions (Kwun *et al.*, 2009; Carter *et al.*, 2013). The late region expresses major and minor capsid proteins, VP1 and VP2, respectively, and includes a miRNA believed to modulate early gene expression (Seo *et al.*, 2009; Schowalter *et al.*, 2011).

In MCPyV-positive Merkel cell carcinoma (MCC), the MCPyV genome integrates into the host DNA while preserving the functions of its early promoter and partially expressing its T antigens (Feng *et al.*, 2008). However, viral MCCs commonly exhibit point mutations in other genome regions, and truncations in the MCPyV LT C-terminal domain (Liu *et al.*, 2016a). The expression of viral oncoproteins primarily relies on the preserved MCPyV promoter rather than endogenous promoters, although there are conflicting reports on whether MCPyV is more likely to integrate into specific chromatin regions (Doolittle-Hall *et al.*, 2015; Czech-Sioli *et al.*, 2020). Analysis of integration sites in multiple MCC tumors reveals that the initial recombination of a linearized MCPyV genome with the host genome may lead to transient circularization and amplification of both the viral genome and adjacent host DNA (Starrett *et al.*, 2017). Differences in viral genome copy number and duplications of host sequences are attributed to the extent of amplification and the site of DNA repair.

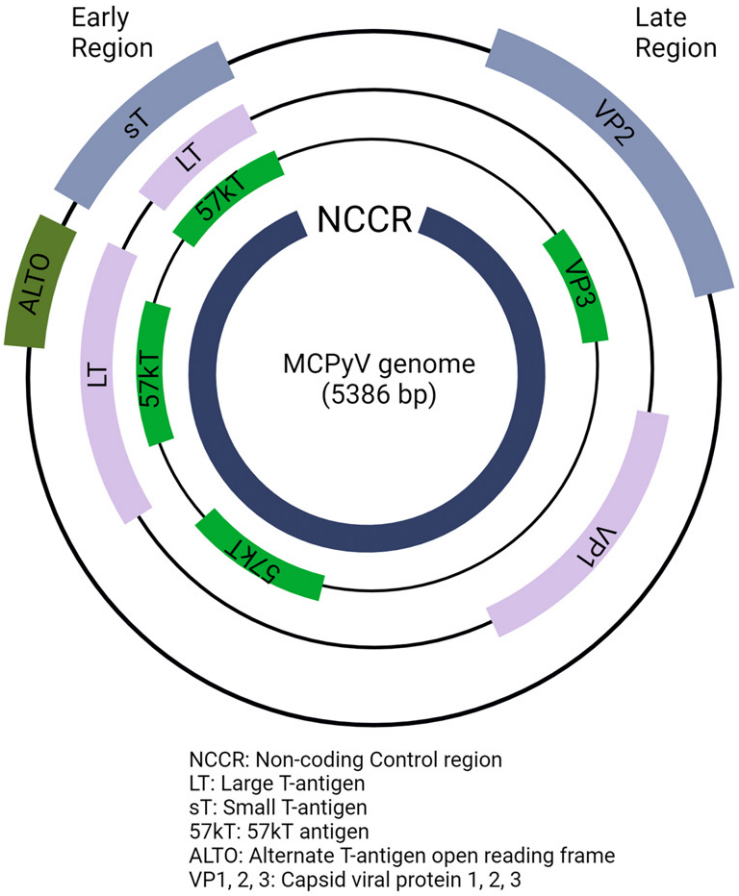


Fig. 6 Genomic map of MCPyV (Sourvinos *et al.*, 2015). Merkel cell polyomavirus (MCPyV) has a 5387 bp circular double-stranded DNA genome with two transcriptional units, the early and late regions. The early region yields four spliced mRNAs encoding four proteins: two alternatively spliced isoforms of the large T antigen (LT and LT', which is also known as 57 kT), the small T antigen (ST) and ALTO (alternate frame of the LT open reading frame). The late region encodes two viral coat proteins, VP1 and VP2, and a microRNA that targets the T antigen transcripts (Created with Biorender.com.).

Origin of MCC

The precise origin of Merkel cell carcinoma (MCC) is a subject of ongoing debate, despite its name suggesting a connection to Merkel cells. The notion that MCC stems from differentiated Merkel cells is questioned due to their post-mitotic nature, limiting oncogenic potential, and the fact that they arise in the epidermis, whereas MCCs predominantly occur in the dermis or subcutis layers (Toker, 1972). Alternately, suggestions propose that MCCs might originate from Merkel cell progenitor cells located at the hair follicle (Zur Hausen *et al.*, 2013; Sauer *et al.*, 2017; Kervarrec *et al.*, 2019). Similarly, progenitor cells from the neural crest have been implicated, as MCPyV-positive MCC cell lines, when cocultured with keratinocytes, undergo neuronal morphological differentiation, dependent on MCPyV LT upregulation of SRY-box transcription factor 2 (Sox2) and atonal bHLH transcription factor 1 (Atoh1) (Harold *et al.*, 2019).

Others posit an epithelial origin for MCC, citing rare cases of epithelial MCCs (Narisawa *et al.*, 2021; Song *et al.*, 2020). Advocates for an epithelial origin point to instances of combined MCC and trichoblastoma tumors sharing somatic mutations, suggesting a potential transition from early to late MCC carcinogenesis with integrated MCPyV genome cells predominating (Kervarrec *et al.*, 2020). The same group found that expressing MCPyV sT and GLI1 in keratinocytes resulted in an MCC-like phenotype, including CK20 expression (Kervarrec *et al.*, 2020). A mouse model expressing MCPyV sT and Atoh in keratinocytes has been developed, resulting in the development of several MCC markers and characteristics in the epidermal layer (Verhaegen *et al.*, 2017).

There is also an argument suggesting that pre/pro B cells may be the source of MCC, as MCC cells consistently express B-lymphoid lineage markers like Paired Box 5 (Pax5) and Terminal deoxynucleotidyl transferase (TdT) (Zur Hausen *et al.*, 2013; Sauer *et al.*, 2017). However, the similarity in cell expression could be coincidental, as it is proposed that epigenetic changes in the cell of origin may lead to significant transcriptional and phenotypic changes resembling Merkel cells. Some even propose that MCPyV-positive and -negative carcinomas may have distinct cells of origin converging on a common phenotype through epigenetic reprogramming. Under normal developmental conditions, the loss of polycomb repressive complex 2 (PRC2) and subsequent reduction in H3K27me3 marks enable the differentiation of Merkel cells in mice (Bardot *et al.*, 2013). Considering this, some researchers reason that the development of MCC may involve a similar change in the epigenome of the unidentified cell of origin, finding that pure MCPyV-positive MCCs were more likely to have lower H3K27me3 than MCPyV-negative tumors (Busam *et al.*, 2017). However, conflicting evidence suggests that virus-negative MCCs, especially those with combined squamous cell carcinomas, had lower H3K27me3 marks than MCPyV-positive MCCs (Matsushita *et al.*, 2017).

MCC Development Through MCPyV Dysbiosis

MCPyV commonly infects the skin of individuals without presenting noticeable symptoms, and it is often shed from the skin (Pastrana *et al.*, 2009). The strategies that drive MCPyV to infect a significant portion of the population without apparent symptoms for extended periods remain unclear (Chen *et al.*, 2011). The fortuitous discovery that human dermal fibroblasts can support MCPyV infection has allowed us to recently explore the MCPyV infectious cycle and its implications for the host cell (Krump *et al.*, 2021; Liu *et al.*, 2016b). By comprehending the circumstances in which MCPyV may struggle to maintain equilibrium with the host immune system, we can potentially deduce the events leading to MCPyV integration and oncogenesis.

In healthy human hosts, there may be a sustained but low basal rate of MCPyV activity in fibroblasts that evades immune recognition, given that early events such as viral entry and trafficking in vitro did not activate interferon-stimulated genes (ISGs) (Krump *et al.*, 2021). In situations where the host's skin experiences abrasion or UV light irradiation, damaged keratinocytes release growth factors and WNT agonists, leading to expression of matrix metalloproteinases (MMPs) and expansion of fibroblasts (Gill and Parks, 2008; Whyte *et al.*, 2012). These changes in the tissue environment could trigger MCPyV early gene expression and DNA synthesis (Liu *et al.*, 2016b).

Under such circumstances, MCPyV pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) present during later stages of infection may upregulate ISGs and inflammatory cytokines, thereby restricting viral replication (Krump *et al.*, 2021). Serological evidence implies that adaptive immune responses, particularly antibodies, could also serve as a significant restriction factor in response to increased MCPyV loads (Faust *et al.*, 2011). The proliferation of dermal fibroblasts and their migration to wounded tissue or the shedding of sunburned skin layers could potentially facilitate MCPyV transmission to new hosts. The antiviral state induced by ISGs, innate cytokine signaling, and immune cells recruited to the wound site would work to restrict and clear cells with high levels of MCPyV infection. A return to a persistent, low-level MCPyV infection could be achieved by infected resident skin cells that manage to avoid immune detection.

The molecular processes linking MCPyV infection to the development of Merkel cell carcinoma (MCC) bear resemblance to those underlying malignancies caused by human papillomaviruses (HPVs). In non-malignant human cells, HPVs, like MCPyV, typically replicate and maintain their genomes as episomes (You, 2010; You *et al.*, 2004; Wang *et al.*, 2013). During persistent infection, a compromised immune system or other pathological conditions may lead to robust viral replication, facilitating the integration of viral genomes into the host DNA. Another parallel between MCPyV and HPV oncogenic mechanisms is that the integrated viral genomes typically lose their ability to replicate, but the non-replicating viral genomes retain the capacity to express viral oncogenes, such as LTT/sT (encoded by MCPyV) and E6/E7 (encoded by HPV) (Krump and You, 2021). These viral oncoproteins promote cellular proliferation and malignant transformation by inhibiting host tumor suppressors such as RB and p53 (Gaglia and Munger, 2018). Uncontrolled cellular proliferation could lead to oncogenesis by allowing virally induced

precancerous lesions to persist and expand. Additionally, viral oncogenes encoded by integrated MCPyV and HPV genomes share the ability to induce genomic instability (Gaglia and Munger, 2018), introducing more DNA breaks in the host genome to facilitate viral genome integration. The hyperproliferation and DNA damage induced by viral oncogenes and/or U.V. irradiation may enable emerging tumor cells to accumulate additional genetic mutations necessary for the development into invasive tumors.

Future Perspective and Treatment

Although over 90% of Merkel cell carcinoma (MCC) patients do not meet the clinical criteria to be categorized as immune compromised, the majority are aged over 50 and exhibit low melanin content in their skin (Heath *et al.*, 2008). Therefore, understanding the impact of UV radiation and aging on the skin could unveil crucial aspects of the early events in MCPyV-associated MCC. Further exploration of the tactics employed by MCPyV to manipulate the host immune system, promoting its own propagation, and driving cellular transformation, is likely to provide new insights into the mechanisms behind MCPyV tumorigenesis.

The growth of cancer therapies aimed at activating and directing immune responses to malignancies instills hope for the treatment of MCC and other viral cancers. However, gaps in our understanding of the biology driving MCPyV-related oncogenesis and MCC's ability to escape the immune system could broaden the range of patients responsive to treatments and enhance the durability of those responses. Addressing some of our knowledge gaps will require technological advances, such as improved detection of low-copy-number viral DNA genomes in tissue isolates or accurate animal models of MCPyV infection. Until then, we can make progress in our investigation by leveraging the wealth of knowledge on human skin and cancer biology and expanding the *in vitro* MCPyV infection model system. Applying this knowledge to reestablish asymptomatic equilibrium between the host and MCPyV in at-risk individuals has the potential to reduce the incidence and increase therapeutic options for MCC.

Conclusion

Viruses have developed various methods to exploit and manipulate the cellular machinery of their hosts for replication. Conversely, hosts have evolved mechanisms to safeguard the cellular environment and sustain essential functions. This book chapter explored how the balance between host and pathogen control of growth signaling pathways, genome maintenance, and immune surveillance determines the outcome of infections. Persistent infections by oncogenic viruses can reach an equilibrium where both parties coexist without symptoms. However, disruptions caused by infection events, immune suppression, or DNA damage can upset this balance. In such cases, viral strategies that support infection can inadvertently promote uncontrolled cell growth, mutation accumulation, and evasion of antitumor immunity, leading to tumorigenesis. Understanding these mechanisms and their contexts is crucial for preventing and treating viral-related cancers.

Oncogenic viruses have played a vital role in revealing fundamental aspects of cellular function and disease. Recent advancements indicate that they continue to be valuable tools for conducting basic research. For example, they have shown that seemingly separate cellular processes are interconnected. There is a proposed overlap between tumor suppression and innate immune signaling pathways, as both can trigger cell cycle arrest and host cell death during infection. By targeting key cellular components at the interface of these pathways, oncogenic viruses can disable host antiviral and anticancer mechanisms, priming infected cells for cancerous transformation. Innate immune responses to intracellular pathogens also act as early tumor suppression measures, highlighting how viral oncogenesis is linked to immune evasion strategies. Given the role of inflammation in later stages of cancer, understanding how viral factors interact with innate responses can clarify this complex aspect of cancer development. Recent research also shows that DNA introduced by viral infection and DNA damage from viral proliferation can activate innate immune DNA sensing pathways, leading to cytokine production with antiviral and antitumor effects. Investigating the coordination of DNA damage responses with immune signaling pathways during oncogenic progression and viral manipulation promises exciting insights.

The seven viruses known to cause cancer in humans employ diverse replication and transmission strategies but are all adept at maintaining chronic infections. This adaptation for prolonged coexistence with a single host necessitates continual manipulation of immunity and cell fate. In contrast, viruses causing acute or self-limiting infections do not persist long enough to induce metastatic disease.

Despite evolving to persist within hosts for years, oncogenic viruses face selective pressure to spread to new hosts while avoiding cancer induction. This explains why they typically do not cause cancer during most infections but may do so after prolonged periods. During years of minimal pathology, shifts in factors enabling host-virus coexistence can lead to viral strategies affecting cell growth and survival, culminating in neoplasms. Understanding how immune suppression disrupts the host-pathogen interplay to result in cancer will be pivotal for future discussions. Inadequate immune surveillance may allow unchecked viral replication and viral effectors that disturb host cell proliferation. Additionally, the overlap in immune responses to tumors and viruses suggests that healthy immune systems can eliminate early transformed cells but may falter under compromised conditions.

Every cancer has complex factors involved in its initiation and progression, making them difficult to treat effectively. Therefore, a logical strategy to prevent or treat cancers caused by viruses is to target the virus itself. This approach has been validated by successful clinical outcomes that significantly reduced the impact of viral cancers. Advancements in antiviral therapy targeting the HCV RNA-dependent RNA polymerase have notably decreased drug side effects while effectively treating HCV infections and

preventing HCC. Vaccines against HPV and HBV have also significantly decreased the incidence of associated cancers in populations with access to these vaccines. In addition to preventive measures, enhancing immune response in "cold" viral tumors (which evoke little to no immune reaction) has proven to be a successful tactic. Utilizing anti-PD1–PDL1 immune checkpoint blockade, a general activator of T cell killing, in individuals with MCPyV+ MCC has shown improved survival rates. The application of this promising therapy in MCC and other viral tumors supports the notion that viral elements may suppress immune responses within the tumor microenvironment. Developing targeted chemotherapies or immunotherapies specific to the oncogenic or immune-suppressive mechanisms induced by viruses could lead to even better clinical outcomes.

Recent advancements in omics technologies have made it more feasible to explore novel therapies for viral cancers and conduct basic research on virus-host interactions. For instance, deep sequencing and gene expression profiling have led to the discovery of MCPyV and a deeper understanding of how oncogenic viruses impact the microRNA environment during oncogenesis. The integration of high-throughput technologies with big data platforms enables researchers to unravel viral oncogenic mechanisms swiftly and efficiently at the omics level. These comprehensive studies will uncover new drug targets, advancing the development of innovative intervention strategies for viral malignancies and shedding light on the interplay between host and pathogen during infection and oncogenesis.

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