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REVIEW ARTICLE

Critical involvement of circular RNAs in virus-associated cancers

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Abstract Virus-related cancer is cancer where viral infection leads to the malignant transformation of the host's infected cells. Seven viruses (e.g., human papillomavirus (HPV), Epstein–Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human T-lymphotropic virus (HTLV), and Merkel cell polyomavirus (MCV)) that infect humans have been identified as an oncogene and have been associated with several human malignancies. Recently, growing attention has been attracted to exploring the pathogenesis of virus-related cancers. One of the most mysterious molecules involved in carcinogenesis and progression of virus-related cancers is circular RNAs (circRNA). These emerging non-coding RNAs (ncRNAs), due to the absence of 5′ and 3′ ends, have high stability than linear RNAs and are found in some species across the eukaryotic organisms. Compelling evidence has revealed that viruses also encode a repertoire of circRNAs, as well as dysregulation of these viral circRNAs play a critical role in the pathogenesis and progression of different types of virus-related cancers. Therefore, understanding the exact role and function of the virally encoded circRNAs with virus-associated cancers will open a new road for increasing our knowledge about the RNA world. Hence, in this review, we will focus on emerging roles of virus-encoded

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circRNAs in multiple cancers, including cervical cancer, gastric cancer, Merkel cell carcinoma, nasopharyngeal carcinoma, Kaposi cancer, and liver cancer.

Introduction

Virus-associated cancers

Cancer is a major public health problem, with an estimated 1,898,160 newly diagnosed cases in the United States and 608,570 deaths in 2021.[1] When malignant cells invade adjacent sites, cancer progresses, leading to increased tumor heterogeneity as well as invasion and spread of cancer cells.[2] According to worldwide studies, approximately one in every six malignancies has an infectious etiology,[3,4] among which tumor viruses play a critical role.[5]

The International Agency for Research on Cancer (IARC) has classified eleven infections as carcinogenic to humans.[6] In this line, it has been demonstrated that viruses are implicated in the biology of multistep oncogenesis, and they are associated with several cancer symptoms.[7] Conceptually, oncolytic viruses use attenuated viruses to infect tumor cells and generate *de novo* or boost pre-existing native immune responses.[8] Generally, cancer development is a multistep process and oncoviruses are necessary but not sufficient for human carcinogenesis. It has been shown that infection by oncogenic viruses causes approximately 15—20% of all human cancers.[9] Most of the oncolytic viruses exert their effects on the early stage of oncogenesis, involving genetic events that lead to tumor initiation or act at later stages by dysregulation of signaling pathways involved in cell proliferation, apoptosis, replicative immortality, and tumor promotion. The molecular mechanisms through which viral proteins interact with the immune system, as well as the immune evasion that has evolved, are also crucial. Consequently, they can stimulate proinflammatory responses by increasing antigen release/recognition and immune activation to counteract the immune evasiveness of malignant cells. Oncolytic viruses that cause cancer, either direct or indirect carcinogenesis, have been defined based on the following[10,11] A) Viral infection is a major risk factor for carcinogenesis according to epidemiological studies; B) Viral DNA is detectable and can persist in tumor samples; C) in model systems, viral genes have a growth-promoting effect, and D) continuous viral oncogene expression or host gene alteration is required for the development of a malignant phenotype.[12]

To date, seven viruses that infect humans have been identified as oncogenic and have been correlated with multiple human malignancies.[13] These include human papillomavirus (HPV), Epstein—Barr virus (EBV), Kaposi's sarcoma herpesvirus (KSHV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human T-lymphotropic virus (HTLV), and Merkel cell polyomavirus (MCV), the most recent members of the human oncogenic virus families.[14] For instance, HPV sequences have been found in virtually all cervical carcinomas and a subset of head and neck squamous cell carcinomas. In addition, HBV and HCV sequences have been reported in a subset of liver carcinomas, and EBV gene expression has been elucidated in a subset of gastric carcinomas.[15—23] Oncogenic viruses cause tumors by producing transforming proteins or non-coding RNAs (ncRNAs) that affect cell biology by acting on critical cellular targets.[24] At least one oncogene is encoded by each known human tumorigenic viruses.[25] The interaction of host and viral elements is an intricate process that generates oncogenesis.[14]

Insights into circular RNAs

Circular RNAs (circRNAs) are a new endogenous sub-class of non-coding RNAs (ncRNAs) composed by reverse splicing of exon—exon junctions of an RNA molecule. This type of RNA includes closed loops of single-stranded RNAs and do not have a free 5′ cap or 3′ poly (A) tail.[26,27] At the first time, circRNAs were observed in viruses by Sanger et al in 1976 and were later described in eukaryotes by Nigro et al in 1991. From 2012 onwards, advanced studies of circRNAs in mammals began with the developing bioinformatics and RNA sequencing technology.[28,29] More than 32,000 circRNAs have been identified in humans, which plays important roles in a variety of biological processes such as regulation of transcription, protein translation, acting as prognostic biomarkers and microRNA sponges (to inhibit the activity of miRNAs), combining with RNA binding proteins, cell differentiation, affecting the function of various cell types, and progression of many diseases including tumor.[30,31] They have several prominent characteristics, including lack of 5′ or 3′ ends and predominant presence in the cytoplasm. Furthermore, abundance and diversity, stability in structure, and a high degree of conservation are other features of these ncRNAs. CircRNAs are more resistant than linear RNAs against exonucleases (including RNase R) destruction because of their lack of 5′ or 3′ end.[32,33]

According to their source, circRNAs are divided into five different types: 1) intron-derived circRNAs (ciRNAs), which consist only of introns and are located in the nucleus; 2) exon-derived circRNAs (ecRNAs), which consist only of exons, and are located in the cytoplasm; 3) exon-intron-derived circRNAs (EIciRNAs) which consist of both exons and introns and are located in the nucleus; 4) intergenic circRNAs; and 5) tRNA intronic circRNAs (tricRNAs) which are formed by splicing pre-tRNA intron. Most of the circRNAs discovered are exon-derived circRNAs (ecRNAs) which are about ~80% of total circRNAs.[32,34,35]

In linear pre-mRNA structures, splicing occurs by removing introns and joining of donor splice site of an exon

(3′ hydroxyl of the upstream exon) to an acceptor splice site of a downstream exon (5′ phosphate end) by a 3′-5′ phosphodiester bond, eventually leading to the generation of a mature mRNA. In these structures, there is a free 5′ phosphate end and a free 3′ hydroxyl end, which are the so-called canonical splice sites or alternative linear splicing.[36,37] Unlike linear RNAs, in circRNA structures, exon/intron to exon or/and intron connection of a pre-mRNA molecule is usually in the form of a covalent interaction of a donor splice site of a downstream exon/intron with an acceptor splice site of upstream exon/intron (3′-5′, 5′-3′, and 2′-5′ phosphodiester bond). In such structures, there is no free 5′, 3′ ends, which creates a loop form, and it is known as back/reverse-splicing in the literature.[38,39]

More abundant viral circRNAs (vcircRNAs) are found in cells infected with the herpesviruses because these circRNAs are largely non-immunogenic and without eliciting the adaptive/innate anti-viral immune responses. The vcircRNA is produce by some viral genes through back-splicing, similar to eukaryotic cells. The production of circRNA molecules from pre-mRNAs is done by alternative splicing, a critical post-transcriptional mechanism and one way that the virus could produce multiple products from a single gene. Also, circRNAs can encode by alternative splicing of the viral mRNAs in some different viruses. Alternative splicing usually occurs in the nucleus; therefore, viruses that all replicate within the nucleus may be capable of producing circRNAs such as DNA viruses (e.g., Adenoviridae, Herpesviridae, Hepadnaviridae, Papillomaviridae, and Polyomaviridae) and some RNA viruses (e.g., Bornaviridae, Retroviridae, and Orthomyxoviridae).[40]

vcircRNAs in EBV can be grouped into four categories based on their parental gene loci, including RPMS1 locus with sixteen vcircRNAs within the BamHI A rightward transcript (BART) region, EBNA latency locus with three vcircRNAs are derived from the EBNA latency locus, LMP2 locus with eight vcircRNAs were derived from the LMP2 locus, and BHLF1 locus (circBHLF1) is derived from the intra-exonic back-splicing of the BHLF1 gene.[41]

Back-splicing is regulated by the cis-regulatory factors (including splice sites and intronic complementary sequences (ICSs)) and the trans-acting elements (including spliceosome factors, cleavage factors, RNA helicases, and RNA-binding proteins (RBP) such as the RNA specific adenosine deaminase (ADAR1), the KH domain-containing RNA binding factor (QKI), and muscleblind-like splicing regulator 1 (MBL)).[39,42]

CircRNAs demonstrate diverse expression patterns in various mammalian cells, including brain, heart, lung, neuron, and tumor cell lines, and play an important biological role in the development and progress of diseases such as cancer.[43,44] For example, circRNAs can act as miRNA sponges such as CDR1 (cerebral degeneration related protein 1), which regulates miR-671, and miRNA-7 in the brain and circHIPK3 (home domain interacting protein kinase 3), which regulates miR-124 in cancer cell lines. Also, like a sponge, circ_0055,625 regulates miR-106b in colon cancer while hsa-circRNA regulates miR532—3p/FOXO4 axis in colorectal cancer.[28,39] Recent studies report that viruses encode a variety of circRNAs.[45] In 2018, virus-encoded circRNAs were discovered in the human herpes simplex viruses, Epstein—Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), and in the human papillomavirus (HPV) in 2019.[46—48] The first viral circular RNA database, VirusCircBase, was introduced in 2020.[49] In this review, we will discuss the emerging role of circRNAs in different virus-related cancers including, cervical cancer, gastric cancer, Merkel cell carcinoma, nasopharyngeal carcinoma, Kaposi sarcoma cancer, and liver cancer.

Crosstalk between circRNAs and virus-related cancers

CircRNAs, as an emerging group of ncRNAs, have unique features implicated in carcinogenesis and progression of virus-related malignancies. Following several virus infections, virus-related circRNAs and/or differently expressed host circular RNAs have been discovered. Hence, circRNAs may play a crucial role in virus infection and host defense. The expression of viral circRNAs is recapitulated across cancer types and patients, where their expression presumably contributes to the tumor phenotype in an immunologically transparent mode.[45] Two main mechanisms have been suggested for the involvement of circRNAs in the pathogenesis and progression of various cancers, including regulation of virus replication via mediating host—virus interaction, induction of antiviral immune response.[50] In this line, there is accumulating evidence that viral circRNAs are abundantly expressed and are found to involve in the pathogenesis of different types of cancers.[47] Several investigations also revealed that host circRNAs are implicated in immune responses against virus infections with either a proviral or antiviral role.[45] It has also been reported that the host circRNAs play a critical function in immunosurveillance.[51] In this section, we will focus on the involvement of viral circRNAs in the pathogenesis of cancers (Fig. 1).

The emerging role of circRNAs in virus-related cervical cancer

Cervical cancer is a type of cancer that develops in the cervix.[52] This cancer was projected to cause 604,000 new cases and 342,000 deaths in 2020, making it the seventh most common cancer worldwide.[53] It is a frequent malignancy in women and accounts for 7.5 percent of cancer-related deaths.[54] Cervical cancer is mainly caused by HPV, but it is not the only cause.[55] HPV is an unenveloped DNA virus found not only in the urinary tract and the vagina but also in the mouth and throat.[56,57] This papillomavirus is the most common sexually transmitted virus and viral infection of the reproductive tract.[58] Although the vast majority of HPV infections are asymptomatic or result in benign lesions, a small number of high-risk HPVs can cause cervical, vulvovaginal, anal, oropharyngeal, and penile malignancies.[59] HPV has been classified as a group 1 carcinogen by the IARC Monographs, including 12 oncogenic forms.[60] HPV DNA is detected in 99.7% of cervical carcinomas, with oncogenic HPV types 16 and 18 accounting for nearly 70% of all cases.[61] In recent years, several studies have been conducted emphasizing the importance of the virus's persistence in developing invasive cervical cancer.[62] The protein products of the viral oncogene E6/E7 can inactivate the cellular proteins p53 and retinoblastoma protein (pRb), leading to disruption of apoptosis and cell cycle regulation,

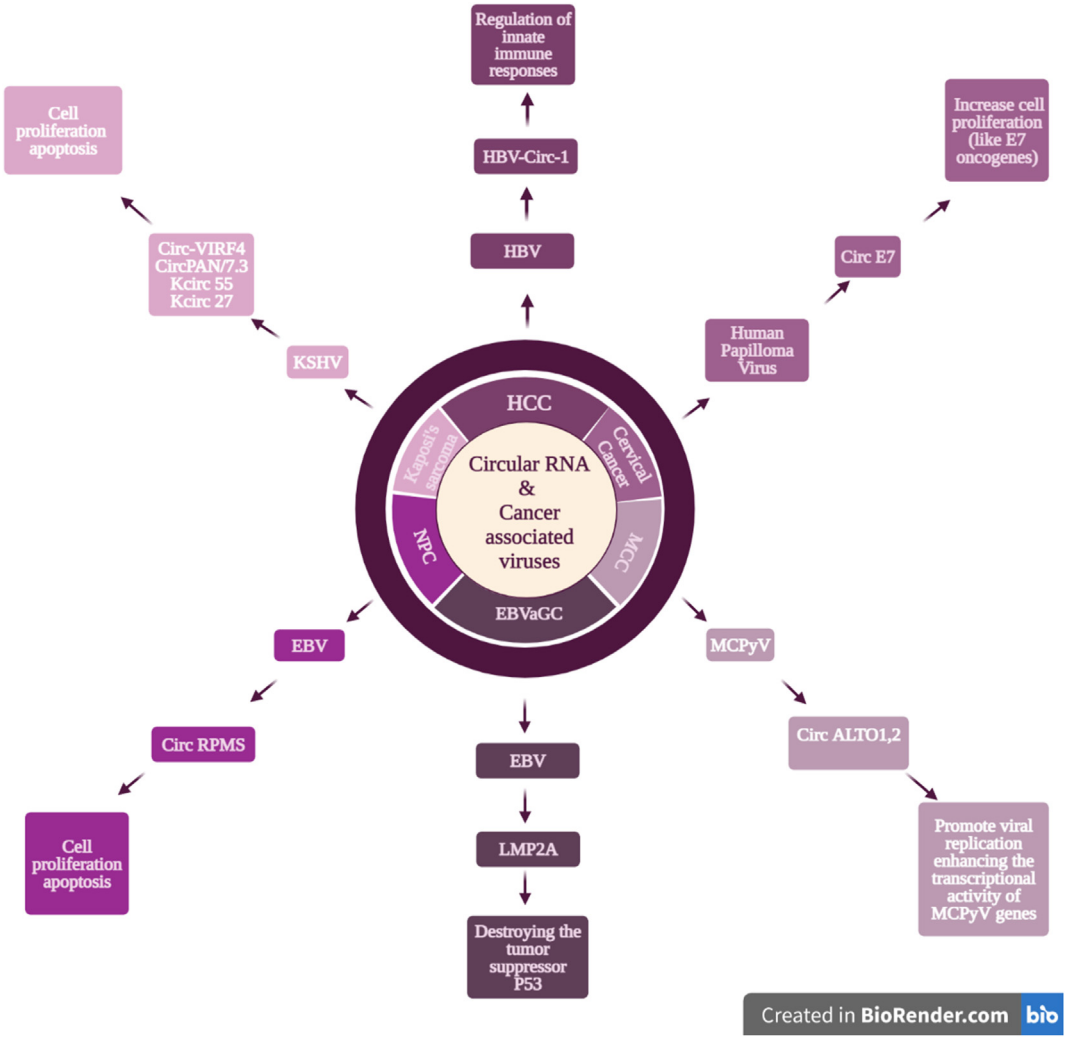

Figure 1 Mechanism of viral circRNAs during viral infection and their correlations with EBV-associated gastric cancer (EBVaGC), Merkel cell carcinoma (MCC), cervical cancer, nasopharyngeal carcinoma (NPC), and Kaposi cancer. Abbreviations: Hepatitis B virus (HBV), Merkelcell polyomavirus (MCPyV), Epstein—Barr virus (EBV).

thus increasing the resistance of tumor cells to various conditions.[63,64] Besides, several viral circRNAs have been shown to play a role in cancer development.[49]

CircRNAs are involved in the carcinogenesis and progression of HPV-related malignancies.[65] These types of ncRNAs have been found from high-risk HPV.[48] Zhao et al discovered that the circular RNA of HPV - circE7 - is preferentially localized in the cytoplasm and that circE7 can be modified by N6-methyladenosine (m6A) and translated to the E7 oncoprotein.[48] According to The Cancer Genome Atlas (TCGA), HPV-derived circE7 is widely expressed in cervical and head and neck malignancies, and HPV16 circE7 is required for transformation of CaSki cells (cervical cancer cell line with integrated HPV16).[48,66] Production of the E7 oncoprotein upregulates p53 activity and promotes apoptosis in the absence of E6.[67,68] Therefore, the low translational activity of circE7, together with the well-established stability of circRNAs, may be particularly suited to promote the fitness of infected cells during the latency period.[48] Circ-E7, which accounts for about 1—3 percent of total E7 transcript, is expressed in HPV16-positive CaSki cells, and its disruption causes decreased E7 oncoprotein levels and slow cell proliferation.[48] This circular RNA was found in TCGA RNA-Seq data from HPV-positive tumors and cell lines exclusively harboring episomal HPVs. Based on this evidence, it is clear that virus-derived protein-coding circular RNAs are biologically active and associated with the transforming properties of various HPVs.[48] CircE7 could be used as a biomarker in HPV-related cancers.[69] Although much of the research on the role of circRNAs in HPV-associated malignancies has focused on cervical cancer, the evolution of circRNAs is still poorly understood concerning the mechanisms that control them and how they differ from the production of linear RNAs.

The emerging role of circRNAs in virus-related gastric cancer

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer death worldwide,[70] with more than 1 million new cases being diagnosed each year.[71]

IARC, GLOBOCAN project, estimates 1,033,701 new cases of gastric cancer and 782,685 deaths related to gastric cancer in 2018.[72,73] Increasing data suggest that several environmental risk factors, such as smoking, alcohol consumption, socioeconomic status, dietary factors, and microbial infections, particularly *Helicobacter pylori* infection and EBV infection, play a role in gastric cancer development.[74,75] The TCGA research network describes four subtypes of gastric cancers: EBV-associated tumors, microsatellite unstable (MSI) tumors, gnomically stable tumors (GS), and chromosomally unstable (CIN) tumors.[76,77]

EBV-associated gastric cancer (EBVaGC), is responsible for up to 10 percent of all molecular subtypes of gastric cancer.[78] This herpesvirus type synthesizes a variety of essential viral ncRNAs that regulate several biological processes, including viral replication, host immune evasion, and cellular transformation.[74,79] EBV generates a variety of viral circRNAs genes such as EBNA, BXLF2, LF1, RPMS1, and LMP2 in different cell lineages with variable degrees of latency between latent and lytic cycles.[46,80] Some of them are critical for maintaining tumor phenotype.[81] Evidence shows circRNAs encoded by EBV genomes have been identified in EBV-positive posttransplant lymphoproliferative disease (PTLD), gastric cancer, and various latently infected B cell lines. These circRNAs are associated with EBV-encoded oncogenic genes such as, LMP2, RPMS1, and BART.[46,82] Based on a recent study by Gong et al analysis of highly malignant SNU-4th cells isolated from gastric cancer xenografts showed that EBV circLMP2A, originating from exon 3 to exon 5 of the LMP2A gene, significantly increased in EBVaGC CSCs (cancer-initiating cells leading to tumor growth, metastasis, and treatment resistance). This circular RNA played a key role in developing stem cell phenotype by reducing the anti-carcinogenic effect of miR-3908, TRIM59 (tripartite motif-containing protein 59), and p53 elements.[81] The biogenesis of circLMP2A is thought to be supported by tissue-specific splicing factors.[41] CircLMP2A has three predicted miR-3908 binding sites, with sites 1 and 3 critical for its sponging ability. CircLMP2A-mediated sponging of miR-3908 releases the miRNA target, TRIM59, an E3 ligase that potentially ubiquitinates and destroys the tumor suppressor p53.[83] The increased expression of EBV-circLMP2A was associated with metastasis and poor prognosis, suggesting that it could be used as a diagnostic and therapeutic target.

The emerging role of circRNAs in virus-related merkel cell carcinoma

Merkel cell carcinoma (MCC) is a form of neuroendocrine skin cancer that is exceptionally aggressive.[84] A solitary cutaneous or subcutaneous nodule, usually in sun-exposed regions, is the common sign of MCC.[85] It is a rare form of skin cancer with an increasing incidence.[86] Between 2000 and 2013, the incidence of MCC nearly doubled in the United States and is expected to exceed 3000 cases per year by 2025, with similar increases expected in Australia and several European countries.[84,87–89] MCC is frequently metastatic, with a disease-specific mortality rate of 33–46%.[90,91] Old age, immunosuppression, sun exposure, and Merkel cell polyomavirus infection are the MCC risk factors.[92] Approximately 80% of MCC cases are caused by MCPyV.[93,94] MCPyV belongs to the Polyomaviridae, a family of naked viruses with circular double-stranded DNA genome (approximately 5 kb).[95,96] Small T antigen (STA), large T antigen (LTA), and the alternative large T antigen open reading frame (ALTO) are encoded by the early region of polyomavirus (ER), whereas the late structural proteins VP1 and VP2 are encoded by the late region of polyomavirus genome.[94,95,97–100] As with other human polyomaviruses, the MCPyV LT antigen contains many domains that play critical roles in viral genome replication, transcription, and carcinogenesis.[101]

In a 2020 study by Abere and colleagues, circRNA back–splice junctions (BSJs) were detected in polyomaviruses using sequencing technology.[102] Another study by Yang et al identified both MCPyV- and Trichodysplasia spinulosa polyomavirus (TSPyV)-derived protein-coding circALTO RNAs. MCPyV has two circRNAs (circALTO1 and circALTO2) in the early region surrounding the ALTO gene, which has been identified in virus-positive Merkel cell carcinoma (VP -MCC) cell lines and patient tumors.[103] ALTO and murine polyomavirus middle T antigen (MTA) have a similar evolutionary origin.[100,104] MCPyV MTA enhances the promoters of transcription genes required for MCPyV replication. Polyomavirus enhancer A binding proteins 1 and 3 bind to these promoters.[105,106] MCPyV circALTO, like MCPyV MTA, can enhance the transcriptional activity of certain promoters, as first shown by Yang et al. Translation of circRNA is supported by internal ribosome entry sequences (IRES), m6A motifs, and novel sequences in the untranslated region (UTR).[107,108] Because circALTOs are m^6A-modified, knocking down Mettl3 and lowering m^6A levels has no apparent effect on ALTO protein levels.[103] However, further research on circALTO could lead to new treatments for HPyV infection or carcinogenesis, as well as a better knowledge of how circRNA metabolism and the polyomavirus life cycle are regulated.

The emerging role of circRNAs in virus-related nasopharyngeal carcinoma (NPC)

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma emerging from the nasopharyngeal mucosal layer. NPC has a different geological distribution, and it is prevalent in East and Southeast Asia. However, epidemiological patterns have shown that the incidence of the disease is gradually decreasing, and its mortality rate has reduced significantly.[73] The main causes of NPC include genetic susceptibility, environmental factors, and EBV infection.[109] The association between EBV infection and NPC was first discovered when high titers of serum antibodies against EBV antigens, including viral capsid antigen (VCA) and antigen early diffuse (EAd/BMRF1), had been detected in these patients.[110] The presence of the EBV genome in NPC cells was then shown by *in situ* hybridization (ISH).[111] Although EBV infection could be found in almost every NPC cell,[110] the exact role of EBV in NPC pathogenesis remains an intriguing concept. Previous studies have demonstrated that EBV encodes non-coding RNAs (ncRNAs), including EBV-encoded small RNAs (EBERs), miRNAs, and long non-coding RNAs (lncRNAs)[112–114] that play a critical role in the

development of NPC. These EBV-encoded miRNAs are also becoming valuable biomarkers for the early detection and relapse of NPC.[115]

Among different circRNAs genes encoded by EBV, such as EBNA, BXLF2, LF1, RPMS1, LMP2, and EBNA-2,[80] It has been found that this gamma-herpesvirus encodes circRNAs that contribute to viral oncogenesis. Toptan et al identified EBV and Kaposi's sarcoma herpesvirus encoding circRNAs, including four circBART isoforms. They showed that EBV circular BamHI A rightward transcripts (circBARTs) were expressed in all latent forms of EBV tumors, including all EBV-infected post-transplant lymphoproliferative disease tumors. They also revealed that circRNAs are highly resistant to degradation by exonucleases and can be preserved even in formalin-fixed and paraffin-embedded samples.[82] The EBV-encoded circRNA circRPMS1 includes head-to-tail splicing of exons 2 to 4 of the RPMS1 gene and is localized in the cytoplasm and the nucleus.[116] It has been revealed that cirRPMS1 increases in metastatic NPCs. The knockdown of cirRPMS1 has been reported to inhibit cell proliferation, induce apoptosis, and repress cell invasion in EBV-positive NPC cells.[117] Further investigations elucidated that circRPMS1_E4_E3a is implicated in NPC oncogenesis through the expression of miRNAs, which leads to epithelial—mesenchymal transition (EMT).[117] A recent study also reported that EBV circLMP-2_e5 from LMP-2 gene is expressed upon EBV lytic reactivation in different cell lines; however, the expression of this circRNA is low in NPC cells.[118] The expression of different EBV-circRNAs indicates that they can act as a potential therapeutic target for EBV-associated NPC. This finding provides an essential understanding for the elucidation of the therapeutic use of circRNAs in NPC.

The emerging role of circRNAs in virus-related Kaposi cancer

Kaposi's sarcoma-associated herpesvirus (KSHV)/human herpesvirus 8 (HHV8) causes Kaposi's sarcoma, the most common cancer in untreated HIV-infected individuals, organ transplant recipients, and immunocompromised individuals. KSHV seropositivity ranges from 40% in sub-Saharan Africa to 2%—4% in Northern Europe, Southeast Asia, and the Caribbean, and it is found in around 10% of Mediterranean countries and 5%—20% of patients in the United States.[119,120] In the case effective antiretroviral therapy, KSHV-associated diseases can develop in patients with undetectable HIV viral loads and normal $CD4^+$ T cell counts.[121] KSHV is also one of the human cancer viruses and a group of human viruses that express several viral miRNAs.[122] These viral miRNAs that are expressed during latency regulate viral persistence, disease progression, and host and viral gene expression, which leads to immune evasion.[123—127] Moreover, several KSHV lncRNAs are expressed most abundantly during lytic replication or following *de novo* infection.[128,129]

Recent studies have shown that KSHV encodes circRNAs such as HHV8_circ_Homo_sapiens_1, HHV8_circ_Homo_sapiens_2, HHV8_circ_Homo_sapiens_3, HHV8_circ_Homo_sapiens_4, HHV8_circ_Homo_sapiens_5, HHV8_circ_Homo_sapiens_6.[80,130] Tagawa and colleagues elegantly indicated that KSHV circRNAs could be found in the ORFs of viral the lytic genes, are up-regulated upon lytic cycle, and alter cell proliferation.[122] KSHV circRNAs are mainly derived from the viral interferon regulatory factor 4 (vIRF4)/K10 site, the polyadenylated nuclear site, and the K7.3 site.[47,82] In this respect, high expression of circ-vIRF4 (circ-viral interferon regulatory factor 4 [circ-vIRF4]) from vIRF4 locus has been found in the KSHV-positive patient sample relative to both B-cell lines and *de novo* infected primary vascular and lymphatic endothelial cells (LECs).[131] The function of circvIRF4 is still unknown; however, it has been shown that vIRF4 modulates p53, and Notch signaling.[132] Furthermore, circvIRF4 does not interact with polysomes, implying that peptides are unlikely to be produced from the circular RNA. Surprisingly, the lymph node of the PEL patient who had a poor clinical prognosis revealed very high circvIRF4 expression.[82] Moreover, Bizunesh et al revealed that circ-vIRF4 and circPAN/K7.3 could be packaged into the viral particle, suggesting that viral circRNAs have a potential function in the early stages of primary infection before the onset of the viral transcription program, and may have a role in innate immune regulation and the effective establishment of KSHV infection. They also showed circ-vIRF4 and circPAN/K7.3 are expressed in PEL cell lines, and their expression can be dysregulated depending on the virus life cycle.[133] It has also been illustrated that viral circRNAs are present in the lymph nodes of patients with KSHV-related disorders such as PEL, Kaposi's sarcoma, and multicentric Castleman's disease. The two KSHV encoded circRNAs, kcirc55 and kcirc97, have been associated with cell proliferation, whereas other KSHV-encoded circRNAs have been associated with gene expression during apoptosis and other tumor-related events.[134] Further investigations are needed to determine the exact regulation pattern of viral genes by KSHV circRNAs in expressing cells.

The emerging role of circRNAs in virus-related liver cancer

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and its incidence is growing worldwide. It is anticipated that more than 1 million annual diagnoses of liver cancer by 2025.[135] Cirrhosis and HCC are mostly caused by hepatitis B and C viruses, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD).[136] Indeed, chronic hepatitis B virus (HBV) infection is a major risk factor for HCC, which can cause pathological damage to liver cells and tissues due to the body's immunological response. The risk of hepatitis C virus (HCV) infection has significantly reduced due to the patients achieving sustained virological response (SVR) with antiviral drugs.[137] HCC has the highest incidence and mortality rates in East Asia and Africa, while it is also increasing in diverse parts of Europe and the United States.[138] Even though a vaccine has been licensed, HBV infection continues to be a major global public health issue. In 2019, the World Health Organization estimated 296 million individuals had chronic hepatitis B infection, with 1.5 million new infections each year. Hepatitis B caused an estimated 820,000 deaths in 2019, largely due to cirrhosis and HCC (https://www.who.int/news-room/fact-sheets/detail/hepatitis-b). Therefore, the pathogenesis of HBV

has been a controversial subject of study for many years. EBV encoded several circRNAs including, HBV_circ_Homo_sapiens_1, HBV_circ_Homo_sapiens_2, HBV_circ_Homo_sapiens_3, HBV_circ_Homo_sapiens_4, HBV_circ_Homo_sapiens_5.[80] Recently, a novel circRNA derived from HBV, known as HBV_circ_1, was identified from HBV pgRNA. It has two junction sites: one junction site is formed similarly as the precursor mRNA splicing, and another junction site is similar to homologous recombination.[139] The researchers also showed the existence of HBV_circ_1 in HepG2.2.15 cells and HBV-related HCC tissue. In addition, Sekiba et al recently discovered that a circRNA produced from HBV pgRNA interacts with DExH-Box helicase 9 (DHX9), an RNA helicase implicated in innate immune responses against DNA viruses.[140] DHX9 is known to inhibit circRNA production by preventing complementary sequences from binding, and HBV circRNA production increases when DHX9 is knocked down, while mRNAs necessary for viral protein translation decrease, resulting in a reduction in viral surface proteins.[141] The regulation of HBV circRNA by DHX9 is regarded as a key mechanism in controlling viral circRNA and viral protein levels during HBV infection; however, more investigations are needed to define the exact role of DHX9 in pgRNA circularization.

Concluding remarks

Research into viral circRNAs, especially those cause cancers and host—virus interactions, is still in its infancy, but it is a promising line of research. Indeed, identifying viruses that encode circRNAs after infection adds another layer of complexity to the biology of viruses and raises many interesting questions, especially those concerned with the processes by which circRNAs may enhance pathogenicity. More studies are needed to identify novel viral circRNAs that are dysregulated during viral infection better to understand the role of viral circRNAs in cancer pathogenesis. In addition, such studies are likely to find new therapeutic targets and treatments for viruses that cause cancer and entail variations in circRNA levels.

Conflict of interests

Authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA A Cancer J Clin*. 2021;71(1):7—33.
2. Elgui de Oliveira D, Müller-Coan BG, Pagano JS. Viral carcinogenesis beyond malignant transformation: EBV in the progression of human cancers. *Trends Microbiol*. 2016;24(8):649—664.
3. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118(12):3030—3044.
4. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Global Health*. 2016;4(9):e609—e616.
5. Chang Y, Moore PS, Weiss RA. Human oncogenic viruses: nature and discovery. *Philos Trans R Soc Lond B Biol Sci*. 2017;372(1732):20160264.
6. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens-Part B: biological agents. *Lancet Oncol*. 2009;10(4):321—322.
7. Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. *Cell Host Microbe*. 2014;15(3):266—282.
8. Orange M, Reuter U, Hobohm U. Coley's lessons remembered: augmenting mistletoe therapy. *Integr Cancer Ther*. 2016;15(4):502—511.
9. Zur Hausen H, de Villiers EM. Cancer "causation" by infections—individual contributions and synergistic networks. *Semin Oncol*. 2014;41(6):860—875.
10. White MK, Pagano JS, Khalili K. Viruses and human cancers: a long road of discovery of molecular paradigms. *Clin Microbiol Rev*. 2014;27(3):463—481.
11. Chiocca EA. Oncolytic viruses. *Nat Rev Cancer*. 2002;2(12):938—950.
12. zur Hausen H. Oncogenic DNA viruses. *Oncogene*. 2001;20(54):7820—7823.
13. Zhang X, Zhang Z, Zheng B, He Z, Winberg G, Ernberg I. An update on viral association of human cancers. *Arch Virol*. 2013;158(7):1433—1443.
14. Mui UN, Haley CT, Tyring SK. Viral oncology: molecular biology and pathogenesis. *J Clin Med*. 2017;6(12):111.
15. Park JS, Chee YH, Namkoong SE, et al. Human papillomavirus detection in cervical carcinoma tissues and paraaortic lymph nodes by the polymerase chain reaction. *Gynecol Oncol*. 1994;53(3):344—351.
16. Gipson BJ, Robbins HA, Fakhry C, D'Souza G. Sensitivity and specificity of oral HPV detection for HPV-positive head and neck cancer. *Oral Oncol*. 2018;77:52—56.
17. Eggersmann TK, Baumeister P, Kumbrink J, et al. Oropharyngeal HPV detection techniques in HPV-associated head and neck cancer patients. *Anticancer Res*. 2020;40(4):2117—2123.
18. Furuta M, Tanaka H, Shiraishi Y, et al. Characterization of HBV integration patterns and timing in liver cancer and HBV-infected livers. *Oncotarget*. 2018;9(38):25075—25088.
19. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol*. 2006;45(4):529—538.
20. van Beek J, Zur Hausen A, Klein Kranenbarg E, et al. EBV-positive gastric adenocarcinomas: a distinct clinicopathologic entity with a low frequency of lymph node involvement. *J Clin Oncol*. 2004;22(4):664—670.
21. Sadato D, Ogawa M, Hirama C, et al. Potential prognostic impact of EBV RNA-seq reads in gastric cancer: a reanalysis of the Cancer Genome Atlas cohort. *FEBS Open Bio*. 2020;10(3):455—467.
22. Alijanpour Aghamolkei M, Tabarraei A, Moradi A, Sadeghi F, Yahyapour Y. Detection of human papillomavirus in osophageal squamous cell carcinoma samples in Mazandaran Province, Iran. *Int J Mol Clin Microbiol*. 2017;7(1):741—747.
23. Yahyapour Y, Rahmani R, Alipour M, Alizadeh A, Khademian A, Sadeghi F. Prevalence and association of human papillomavirus, Epstein-Barr virus and Merkel Cell polyomavirus with neoplastic esophageal lesions in northern Iran. *Caspian J Intern Med*. 2018;9(4):353—360.
24. Cantalupo PG, Katz JP, Pipas JM. Viral sequences in human cancer. *Virology*. 2018;513:208—216.
25. Zheng ZM. Viral oncogenes, noncoding RNAs, and RNA splicing in human tumor viruses. *Int J Biol Sci*. 2010;6(7):730—755.
26. Samavarchi Tehrani S, Goodarzi G, Panahi G, Maniati M, Meshkani R. Multiple novel functions of circular RNAs in diabetes mellitus. *Arch Physiol Biochem*. 2021:1—30.

27. Ebrahimpour A, Sarfi M, Rezatabar S, Tehrani SS. Novel insights into the interaction between long non-coding RNAs and microRNAs in glioma. *Mol Cell Biochem*. 2021;476(6):2317—2335.
28. Li J, Xu Q, Huang ZJ, et al. CircRNAs: a new target for the diagnosis and treatment of digestive system neoplasms. *Cell Death Dis*. 2021;12(2):205.
29. Lei M, Zheng G, Ning Q, Zheng J, Dong D. Translation and functional roles of circular RNAs in human cancer. *Mol Cancer*. 2020;19(1):30.
30. Meng X, Li X, Zhang P, Wang J, Zhou Y, Chen M. Circular RNA: an emerging key player in RNA world. *Briefings Bioinf*. 2017;18(4):547—557.
31. Verduci L, Tarcitano E, Strano S, Yarden Y, Blandino G. CircRNAs: role in human diseases and potential use as biomarkers. *Cell Death Dis*. 2021;12(5):468.
32. Li J, Sun D, Pu W, Wang J, Peng Y. Circular RNAs in cancer: biogenesis, function, and clinical significance. *Trends Cancer*. 2020;6(4):319—336.
33. Yu CY, Kuo HC. The emerging roles and functions of circular RNAs and their generation. *J Biomed Sci*. 2019;26(1):29.
34. Lu Z, Filonov GS, Noto JJ, et al. Metazoan tRNA introns generate stable circular RNAs in vivo. *RNA*. 2015;21(9):1554—1565.
35. Geng Y, Jiang J, Wu C. Function and clinical significance of circRNAs in solid tumors. *J Hematol Oncol*. 2018;11(1):98.
36. Li X, Yang L, Chen LL. The biogenesis, functions, and challenges of circular RNAs. *Mol Cell*. 2018;71(3):428—442.
37. Santer L, Bär C, Thum T. Circular RNAs: a novel class of functional RNA molecules with a therapeutic perspective. *Mol Ther*. 2019;27(8):1350—1363.
38. Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol*. 2020;21(8):475—490.
39. Gokool A, Loy CT, Halliday GM, Voineagu I. Circular RNAs: the brain transcriptome comes full circle. *Trends Neurosci*. 2020;43(10):752—766.
40. Nahand JS, Jamshidi S, Hamblin MR, et al. Circular RNAs: new epigenetic signatures in viral infections. *Front Microbiol*. 2020;11:1853.
41. Avilala J, Becnel D, Abdelghani R, et al. Role of virally encoded circular RNAs in the pathogenicity of human oncogenic viruses. *Front Microbiol*. 2021;12:657036.
42. Naeli P, Pourhanifeh MH, Karimzadeh MR, et al. Circular RNAs and gastrointestinal cancers: epigenetic regulators with a prognostic and therapeutic role. *Crit Rev Oncol Hematol*. 2020;145:102854.
43. Aufiero S, Reckman YJ, Pinto YM, Creemers EE. Circular RNAs open a new chapter in cardiovascular biology. *Nat Rev Cardiol*. 2019;16(8):503—514.
44. Tehrani SS, Ebrahimi R, Al-E-Ahmad A, et al. Competing endogenous RNAs (CeRNAs): novel network in neurological disorders. *Curr Med Chem*. 2021;28(29):5983—6010.
45. Tan KE, Lim YY. Viruses join the circular RNA world. *FEBS J*. 2021;288(15):4488—4502.
46. Ungerleider N, Concha M, Lin Z, et al. The Epstein Barr virus circRNAome. *PLoS Pathog*. 2018;14(8):e1007206.
47. Ungerleider NA, Jain V, Wang Y, et al. Comparative analysis of gammaherpesvirus circular RNA repertoires: conserved and unique viral circular RNAs. *J Virol*. 2019;93(6):e01952-18.
48. Zhao J, Lee EE, Kim J, et al. Transforming activity of an oncoprotein-encoding circular RNA from human papillomavirus. *Nat Commun*. 2019;10(1):2300.
49. Cai Z, Fan Y, Zhang Z, et al. VirusCircBase: a database of virus circular RNAs. *Briefings Bioinf*. 2021;22(2):2182—2190.
50. Xie H, Sun H, Mu R, et al. The role of circular RNAs in viral infection and related diseases. *Virus Res*. 2021;291:198205.
51. Li X, Liu CX, Xue W, et al. Coordinated circRNA biogenesis and function with NF90/NF110 in viral infection. *Mol Cell*. 2017;67(2):214—227.
52. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2019;17(1):64—84.
53. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin*. 2021;71(3):209—249.
54. Cancer IAfRo [Internet] 2012. In: *Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. GLOBOCAN*. Lyon: WHO; 2012.
55. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12—19.
56. Eggersmann TK, Sharaf K, Baumeister P, et al. Prevalence of oral HPV infection in cervical HPV positive women and their sexual partners. *Arch Gynecol Obstet*. 2019;299(6):1659—1665.
57. Bosch FX, Muñoz N. The viral etiology of cervical cancer. *Virus Res*. 2002;89(2):183—190.
58. Who. *Human Papillomavirus (HPV) and Cervical Cancer: Fact Sheet*. 2016.
59. Lowy DR, Schiller JT. Reducing HPV-associated cancer globally. *Cancer Prev Res*. 2012;5(1):18—23.
60. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum*. 1995;64:1—378.
61. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA A Cancer J Clin*. 2016;66(1):7—30.
62. Mammas IN, Sourvinos G, Giannoudis A, Spandidos DA. Human papilloma virus (HPV) and host cellular interactions. *Pathol Oncol Res*. 2008;14(4):345—354.
63. Hamid NA, Brown C, Gaston K. The regulation of cell proliferation by the papillomavirus early proteins. *Cell Mol Life Sci*. 2009;66(10):1700—1717.
64. Tungteakkhun SS, Duerksen-Hughes PJ. Cellular binding partners of the human papillomavirus E6 protein. *Arch Virol*. 2008;153(3):397—408.
65. Wang H, Zhao Y, Chen M, Cui J. Identification of novel long non-coding and circular RNAs in human papillomavirus-mediated cervical cancer. *Front Microbiol*. 2017;8:1720.
66. Wu TC, Hsieh ST, Purow BW, Kurman RJ. Demonstration of human papillomavirus (HPV) genomic amplification and viral-like particles from CaSki cell line in SCID mice. *J Virol Methods*. 1997;65(2):287—298.
67. Moody CA, Laimins LA. Human papillomavirus oncoproteins: pathways to transformation. *Nat Rev Cancer*. 2010;10(8):550—560.
68. Jones DL, Thompson DA, Münger K. Destabilization of the RB tumor suppressor protein and stabilization of p53 contribute to HPV type 16 E7-induced apoptosis. *Virology*. 1997;239(1):97—107.
69. Bonelli P, Borrelli A, Tuccillo FM, Buonaguro FM, Tornesello ML. The role of circRNAs in human papillomavirus (HPV)-associated cancers. *Cancers*. 2021;13(5):1173.
70. Wang FH, Zhang XT, Li YF, et al. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. *Cancer Commun*. 2021;41(8):747—795.
71. Thrift AP, El-Serag HB. Burden of gastric cancer. *Clin Gastroenterol Hepatol*. 2020;18(3):534—542.
72. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941—1953.
73. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clin*. 2018;68(6):394—424.

74. Zebardast A, Tehrani SS, Latifi T, Sadeghi F. Critical review of Epstein–Barr virus microRNAs relation with EBV-associated gastric cancer. *J Cell Physiol*. 2021;236(9):6136–6153.
75. Eusebi LH, Telese A, Marasco G, Bazzoli F, Zagari RM. Gastric cancer prevention strategies: a global perspective. *J Gastroenterol Hepatol*. 2020;35(9):1495–1502.
76. Wang Q, Xie Q, Liu Y, et al. Clinical characteristics and prognostic significance of TCGA and ACRG classification in gastric cancer among the Chinese population. *Mol Med Rep*. 2020;22(2):828–840.
77. Chen T, Xu XY, Zhou PH. Emerging molecular classifications and therapeutic implications for gastric cancer. *Chin J Cancer*. 2016;35:49.
78. Ignatova E, Seriak D, Fedyanin M, et al. Epstein–Barr virus-associated gastric cancer: disease that requires special approach. *Gastric Cancer*. 2020;23(6):951–960.
79. Skalsky RL, Cullen BR. EBV noncoding RNAs. *Curr Top Microbiol Immunol*. 2015;391:181–217.
80. Glažar P, Papavasileiou P, Rajewsky N. circBase: a database for circular RNAs. *RNA*. 2014;20(11):1666–1670.
81. Gong Lp, Chen Jn, Dong M, et al. Epstein-Barr virus-derived circular RNA LMP 2A induces stemness in EBV-associated gastric cancer. *EMBO Rep*. 2020;21(10):e49689.
82. Toptan T, Abere B, Nalesnik MA, et al. Circular DNA tumor viruses make circular RNAs. *Proc Natl Acad Sci U S A*. 2018;115(37):E8737–E8745.
83. Rahman MS, Hoque MN, Islam MR, et al. Epitope-based chimeric peptide vaccine design against S, M and E proteins of SARS-CoV-2 etiologic agent of global pandemic COVID-19: an in silico approach. *PeerJ*. 2020;8:e9572.
84. Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol*. 2005;89(1):1–4.
85. Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. *Nat Rev Dis Prim*. 2017;3:17077.
86. Becker M, Dominguez M, Greune L, et al. Infectious entry of merkel cell polyomavirus. *J Virol*. 2019;93(6):e02004–e02018.
87. Fitzgerald TL, Dennis S, Kachare SD, Vohra NA, Wong JH, Zervos EE. Dramatic increase in the incidence and mortality from Merkel cell carcinoma in the United States. *Am Surg*. 2015;81(8):802–806.
88. Youlden DR, Soyer HP, Youl PH, Fritschi L, Baade PD. Incidence and survival for Merkel cell carcinoma in Queensland, Australia, 1993-2010. *JAMA Dermatol*. 2014;150(8):864–872.
89. Zaar O, Gillstedt M, Lindelöf B, Wennberg-Larkö AM, Paoli J. Merkel cell carcinoma incidence is increasing in Sweden. *J Eur Acad Dermatol Venereol*. 2016;30(10):1708–1713.
90. Agelli M, Clegg LX, Becker JC, Rollison DE. The etiology and epidemiology of merkel cell carcinoma. *Curr Probl Cancer*. 2010;34(1):14–37.
91. Harms PW. Update on Merkel cell carcinoma. *Clin Lab Med*. 2017;37(3):485–501.
92. Amaral T, Leiter U, Garbe C. Merkel cell carcinoma: epidemiology, pathogenesis, diagnosis and therapy. *Rev Endocr Metab Disord*. 2017;18(4):517–532.
93. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science*. 2008;319(5866):1096–1100.
94. Shuda M, Feng H, Kwun HJ, et al. T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. *Proc Natl Acad Sci U S A*. 2008;105(42):16272–16277.
95. Moens U, Krumbholz A, Ehlers B, et al. Biology, evolution, and medical importance of polyomaviruses: an update. *Infect Genet Evol*. 2017;54:18–38.
96. Bayer NJ, Januliene D, Zocher G, Stehle T, Moeller A, Blaum BS. Structure of Merkel cell polyomavirus capsid and interaction with its glycosaminoglycan attachment receptor. *J Virol*. 2020;94(20):e01664-19.
97. Houben R, Shuda M, Weinkam R, et al. Merkel cell polyomavirus-infected Merkel cell carcinoma cells require expression of viral T antigens. *J Virol*. 2010;84(14):7064–7072.
98. Schowalter RM, Buck CB. The Merkel cell polyomavirus minor capsid protein. *PLoS Pathog*. 2013;9(8):e1003558.
99. Theiss JM, Günther T, Alawi M, et al. A comprehensive analysis of replicating Merkel cell polyomavirus genomes delineates the viral transcription program and suggests a role for mcv-miR-M1 in episomal persistence. *PLoS Pathog*. 2015;11(7):e1004974.
100. Carter JJ, Daugherty MD, Qi X, et al. Identification of an overprinting gene in Merkel cell polyomavirus provides evolutionary insight into the birth of viral genes. *Proc Natl Acad Sci U S A*. 2013;110(31):12744–12749.
101. Pietropaolo V, Prezioso C, Moens U. Merkel cell polyomavirus and Merkel cell carcinoma. *Cancers*. 2020;12(7):1774.
102. Abere B, Zhou H, Li J, et al. Merkel cell polyomavirus encodes circular RNAs (circRNAs) enabling a dynamic circRNA/microRNA/mRNA regulatory network. *mBio*. 2020;11(6):e03059-20.
103. Jin Y, Yang H, Ji W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses*. 2020;12(4):372.
104. van der Meijden E, Feltkamp M. The human polyomavirus middle and alternative T-antigens; thoughts on roles and relevance to cancer. *Front Microbiol*. 2018;9:398.
105. Gottlieb KA, Villarreal LP. Natural biology of polyomavirus middle T antigen. *Microbiol Mol Biol Rev*. 2001;65(2):288–318.
106. Wasylyk C, Imler JL, Wasylyk B. Transforming but not immortalizing oncogenes activate the transcription factor PEA1. *EMBO J*. 1988;7(8):2475–2483.
107. Pamudurti NR, Bartok O, Jens M, et al. Translation of circRNAs. *Mol Cell*. 2017;66(1):9–21.
108. Tang C, Xie Y, Yu T, et al. m 6 A-dependent biogenesis of circular RNAs in male germ cells. *Cell Res*. 2020;30(3):211–228.
109. Wei WI, Sham JS. Nasopharyngeal carcinoma. *Lancet*. 2005;365(9476):2041–2054.
110. Gunvén P, Klein G, Henle G, Henle W, Clifford P. Epstein-Barr virus in Burkitt's lymphoma and nasopharyngeal carcinoma. Antibodies to EBV associated membrane and viral capsid antigens in Burkitt lymphoma patients. *Nature*. 1970;228(5276):1053–1056.
111. Wolf H, zur Hausen H, Klein G, Becker V, Henle G, Henle W. Attempts to detect virus-specific DNA sequences in human tumors. *Med Microbiol Immunol*. 1975;161(1):15–21.
112. Marquitz AR, Mathur A, Edwards RH, Raab-Traub N. Host gene expression is regulated by two types of noncoding RNAs transcribed from the Epstein-Barr virus BamHI A rightward transcript region. *J Virol*. 2015;89(22):11256–11268.
113. Pfeffer S, Zavolan M, Grässer FA, et al. Identification of virus-encoded microRNAs. *Science*. 2004;304(5671):734–736.
114. Kieff E. Epstein-Barr virus and its replication. *Fields' virology*. 2001:2575–2627.
115. Gao W, Wong TS, Lv KX, Zhang MJ, Tsang RKY, Chan JYW. Detection of Epstein-Barr virus (EBV)-encoded microRNAs in plasma of patients with nasopharyngeal carcinoma. *Head Neck*. 2019;41(3):780–792.
116. Huang JT, Chen JN, Gong LP, et al. Identification of virus-encoded circular RNA. *Virology*. 2019;529:144–151.
117. Liu Q, Shuai M, Xia Y. Knockdown of EBV-encoded circRNA circRPMS1 suppresses nasopharyngeal carcinoma cell proliferation and metastasis through sponging multiple miRNAs. *Cancer Manag Res*. 2019;11:8023–8031.
118. Tan KE, Ng WL, Marinov GK, et al. Identification and characterization of a novel epstein-barr virus-encoded circular RNA from LMP-2 gene. *Sci Rep*. 2021;11(1):14392.

119. Chatlynne LG, Ablashi DV. Seroepidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV). *Semin Cancer Biol*. 1999;9(3):175—185.
120. Yarchoan R, Uldrick TS. HIV-associated cancers and related diseases. *N Engl J Med*. 2018;378(22):2145.
121. Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. *N Engl J Med*. 2007;357(13):1352—1353.
122. Tagawa T, Gao S, Koparde VN, et al. Discovery of Kaposi's sarcoma herpesvirus-encoded circular RNAs and a human antiviral circular RNA. *Proc Natl Acad Sci U S A*. 2018;115(50):12805—12810.
123. Hansen A, Henderson S, Lagos D, et al. KSHV-encoded miRNAs target MAF to induce endothelial cell reprogramming. *Genes Dev*. 2010;24(2):195—205.
124. Lei X, Bai Z, Ye F, Huang Y, Gao SJ. Regulation of herpesvirus lifecycle by viral microRNAs. *Virulence*. 2010;1(5):433—435.
125. Lei X, Bai Z, Ye F, et al. Regulation of NF-kappaB inhibitor IkappaBalpha and viral replication by a KSHV microRNA. *Nat Cell Biol*. 2010;12(2):193—199.
126. Gottwein E, Corcoran DL, Mukherjee N, et al. Viral microRNA targetome of KSHV-infected primary effusion lymphoma cell lines. *Cell Host Microbe*. 2011;10(5):515—526.
127. Qin Z, Freitas E, Sullivan R, et al. Upregulation of xCT by KSHV-encoded microRNAs facilitates KSHV dissemination and persistence in an environment of oxidative stress. *PLoS Pathog*. 2010;6(1):e1000742.
128. Arias C, Weisburd B, Stern-Ginossar N, et al. KSHV 2.0: a comprehensive annotation of the Kaposi's sarcoma-associated herpesvirus genome using next-generation sequencing reveals novel genomic and functional features. *PLoS Pathog*. 2014;10(1):e1003847.
129. Chandriani S, Xu Y, Ganem D. The lytic transcriptome of Kaposi's sarcoma-associated herpesvirus reveals extensive transcription of noncoding regions, including regions antisense to important genes. *J Virol*. 2010;84(16):7934—7942.
130. Grundhoff A, Sullivan CS. Virus-encoded microRNAs. *Virology*. 2011;411(2):325—343.
131. Tagawa T, Oh D, Santos J, et al. Characterizing expression and regulation of gamma-herpesviral circular RNAs. *Front Microbiol*. 2021;12:670542.
132. Baresova P, Pitha PM, Lubyova B. Distinct roles of Kaposi's sarcoma-associated herpesvirus-encoded viral interferon regulatory factors in inflammatory response and cancer. *J Virol*. 2013;87(17):9398—9410.
133. Abere B, Li J, Zhou H, Toptan T, Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus-encoded circRNAs are expressed in infected tumor tissues and are incorporated into virions. *mBio*. 2020;11(1):e03027-19.
134. Panda AC, De S, Grammatikakis I, et al. High-purity circular RNA isolation method (RPAD) reveals vast collection of intronic circRNAs. *Nucleic Acids Res*. 2017;45(12):e116.
135. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Prim*. 2021;7(1):6.
136. Higashi T, Friedman SL, Hoshida Y. Hepatic stellate cells as key target in liver fibrosis. *Adv Drug Deliv Rev*. 2017;121:27—42.
137. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology*. 2017;153(4):996—1005.
138. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19(2):223—238.
139. Zhu M, Liang Z, Pan J, et al. HBV pgRNA can generate a circRNA with two junction sites. *bioRxiv*. 2020.
140. Sekiba K, Otsuka M, Ohno M, et al. DHX9 regulates production of hepatitis B virus-derived circular RNA and viral protein levels. *Oncotarget*. 2018;9(30):20953—20964.
141. Aktaş T, Ilık İA, Maticzka D, et al. DHX9 suppresses RNA processing defects originating from the Alu invasion of the human genome. *Nature*. 2017;544(7648):115—119.