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Review

Viral oncoproteins involved in carcinogenesis

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ABSTRACT

Approximately 10 to 20% of all cancers worldwide can be attributed to infection by viruses. Seven human viruses are known for their ability to cause cancer: Epstein-Barr virus, hepatitis B and C viruses, human papillomavirus, human T-Cell lymphotropic virus, Kaposi's sarcoma human virus, and Merkel cell polyomavirus. These viruses have a common trait of encoding proteins which have growth enhancing activity, cell survival activity, and cell cycle checkpoint bypassing activity. In the context of viral infection, the role of these proteins is mainly to promote cell cycle progression, since viral replication necessitates the cellular machinery. However, the fact that these viral proteins also act in the same fashion as cellular oncogenes allows them to drive abnormal cell proliferation, which can lead to cellular transformation. This review will focus on these virus-encoded proteins. Each of the seven viruses will be briefly introduced, and their viral oncogenes will be presented in regard to their known role in carcinogenesis. Emphasis will be placed on their cellular partners, the pathways that are modulated by those proteins, and the molecular mechanisms behind their ability to drive the development of cancer.

KEYWORDS: cancer, virus, oncogene, tumor suppressor, protein-protein interaction, cell signaling

INTRODUCTION

Cancer has become one of the most important fields of biomedical research of the 21st century. Key studies have helped to understand the basics of carcinogenesis, from how oncogenes become over-activated and drive uncontrolled cell proliferation through the roles of tumor suppressors and anti-apoptotic proteins, tumor microenvironment, alternative splicing dysregulation, and many more. With our increased understanding of these molecular bases, research has also focused on the environmental factors that have the property to potentiate the process of tumorigenesis. These factors, such as alcohol, smoking, bacterial infections, ionizing radiations and many others are also important research subjects in the field of cancer. A better comprehension of how these factors drive the development of tumors is a priority for public health to decrease the prevalence of cancers and to lighten the burden on healthcare systems. Of these agents, viral infection accounts for 10% to 20% of all cancers worldwide, with some viruses being implicated in as much as 99.7% of certain types of cancer [1]. Mainly, seven viruses have well-studied implications in this disease. From these seven, five possess a DNA genome: human papillomavirus, hepatitis B virus, Merkel cell polyomavirus, and two members of the Herpesviridae family, Epstein-Barr virus, and Kaposi's sarcoma human virus. The other two cancer-inducing viruses possess an RNA genome: hepatitis C virus and human T-Cell lymphotropic virus. Interestingly, these viruses encode for proteins that have a similar activity as cellular oncogenes. For example, these proteins can stimulate uncontrolled cellular proliferation, inactivate tumor suppressors, stabilize anti-apoptotic proteins, and enhance the expression of angiogenic factors. This review will focus on those virus-encoded proteins that potentiate the development

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of cancer. Each of the seven viruses will be briefly introduced, and their viral oncoproteins will be presented in regards to their known role in carcinogenesis. Emphasis will be placed on their cellular partners, the pathways that are modulated by those proteins, and the molecular mechanisms behind their ability to drive the development of cancer.

Human papillomavirus

Papillomaviruses are a large family of non-enveloped, double-stranded DNA viruses which infect many different hosts. More than 120 types of human papillomaviruses (HPV) have been identified and classified as either low risk (HPV-6, -11) or high risk (HPV-16, -18) based on their prevalence in cancer *versus* their ability to cause benign lesions such as warts. HPV-16 and 18 are the most studied since their implication in cervical carcinoma (up to 99.7%) has been known for a long time. Moreover, HPV is also present in head and neck cancers and anogenital tract carcinomas, with implications ranging between a fifth to nearly 100% for these cancers [2, 3]. There are mainly two viral products that act as oncogenes upon expression in cells, namely the early proteins E6 and E7. Because of their implication in cell-transforming activities, research studies have mainly focused on them, leading to their extensive biochemical and molecular characterization [4]. These oncoproteins do not possess any enzymatic activity and thus mostly induce cellular modifications through protein-protein interactions [5, 6].

E6, one of HPV early proteins, was rapidly linked to the oncogenic potential of this virus during the initial attempts to understand viral carcinogenesis. The first evidence of a functional role for E6 was demonstrated by lower levels of p53, the well-known tumor suppressor, in cells expressing either HPV 16 DNA or E6 protein [7, 8]. Indeed, E6 can bind to p53 and induce its degradation by the ubiquitin-proteasome pathway [9]. E6-AP (E6-associated protein), a cellular E3 ubiquitin ligase which interacts with E6, is necessary to achieve ubiquitination and degradation of p53 [10, 11]. Recently, the ability of E6 proteins from 29 HPV subtypes to degrade p53 and their potential in oncogenesis have been characterized which showed unexpected variability between E6 from different subtypes [12]. Degradation of p53 leads to major impairments in DNA repair, cell-cycle arrest, and even apoptosis pathways. Moreover, E6 is also able to interact with CBP/p300, two coactivators of numerous transcription factors like p53 and NF-κB, leading to downregulation of transcription [13]. Furthermore, p53 is a repressor of a large number of known genes. As a consequence, the E6-mediated degradation of p53 leads to an enhanced expression of an important number of genes. For instance, survivin, a novel member of the IAP (inhibitor of apoptosis) gene family, was shown to be upregulated by the expression of E6 through such a mechanism [14]. Lately, upregulation of the genomic deaminase APOBEC3B upon E6 expression was also proposed to be caused *via* this mechanism, which leads to DNA damage and mutations in HPV-positive cells [15]. E6 transforming activity is also characterized by transcriptional activation of hTERT, the catalytic subunit of telomerase [16-18]. Telomere erosion leads to senescence or apoptosis, hence the need in cancer cells for active telomerase to achieve immortalization. It has been shown that this enhanced expression is mediated by the interaction of E6 and Myc [19]. Myc and E6 together can bind to the promoter of hTERT and act as an activator of transcription, increasing mRNAs and protein levels of this catalytic subunit. Physical interaction between E6 and the whole telomerase complex inducing enhanced activity independently of transcription was also later demonstrated [20].

The implication of E6 in preventing apoptosis is not limited to the degradation of p53 and overexpression of survivin. Indeed, E6 can induce the degradation of essential proteins involved in TRAIL-mediated apoptosis, like FADD and procaspase 8 [21]. Moreover, E6 and E6-AP together can bind to and induce proteasomal degradation of BAK, thus preventing the mitochondrial apoptotic pathway [22]. Other HPV mechanisms to prevent apoptosis exist and have been reviewed [23]. In addition to preventing apoptosis, HPV E6 also avoids immune response by inhibiting IRF-3 transcriptional activity [24]. Downregulation of the NOTCH1 pathway in HPV-positive cervical cancer cell has also been characterized, but whether it is dependent upon E6 or E7 is still not known [25].

Recently, the interaction between E6 and FHL2 (Four and a half LIM-only protein 2) leading to a change in its subcellular distribution was discovered [26].

Although further studies are still needed, this finding is interesting since FLH-2 is involved in the assembly of extracellular membranes in various pathways such as cell adhesion, survival, and mobility. Finally, it should be noted that there is evidence for a role of E6 in deregulating miRNAs profiles [27, 28] and that numerous additional interaction partners for E6 are known, such as paxillin, tuberin, E6BP, hDlg1, hDlg4, hSCRIB, the MAGI family, hADA3, NFX1, TLR9, TNFR1 and hADA3 amongst others, but the biological relevance in oncogenesis is still unknown for some of them (reviewed in [29]).

Another HPV early protein, E7, showed interesting characteristics when it was first studied, since it interacts with the retinoblastoma gene product (pRB) [30]. Like the large T antigen of SV40 (TAg) and E1A of adenovirus, E7 can disrupt the complex formed by pRB and E2F transcription factors [31]. However, further studies showed that unlike E1A and TAg, E7 mediates the proteasome-dependent degradation of pRB [32]. To achieve this, the cullin 2 ubiquitin ligase complex is necessary, as it can bring pRB to the proteasome through binding of E7 to one of its subunits, the elongin C [33]. Destabilization of pRB releases E2F1, 2 and 3 transcription factors, allowing G1-S transition as they are involved in cell cycle progression. E7 also targets two pRB-related pocket proteins, p107 and p130, for proteasomal degradation which promotes proliferation [32, 34]. Interestingly, the association of E7 with the 600 kDa retinoblastoma-associated factor, p600, has raised evidence of E7 implication in anchorage-independent growth [35]. Similar to E6, E7 binds to p300 as well, leading to the same downregulation of its transcriptional activity [36]. Furthermore, E7 prevents inhibition of CDK2 and cyclin complex by $p21^{Cip1}$ and $p27^{Kip1}$ through binding with these proteins [37-39]. This allows the uncoupling of differentiation and proliferation in infected keratinocytes. Moreover, E7 is able to directly activate the kinase activity of CDK2 complex with either cyclin A or E [40]. Also, the interaction between $p21^{Cip1}$ and E7 releases the inhibition of PCNA-dependent DNA replication [37]. Finally, histone deacetylases (HDACs) are also an interaction target of E7 [41]. For example, E2F2 is overexpressed in HPV infection due to E7 preventing HDACs-mediated deacetylation of its promoter [42].

Although E6-induced increase in hTERT expression and activity has been known for a long time, the implication of E7 in telomerase activation has only been recently shown. E7-mediated degradation of pRB is presumed to leave E2F unable to bind the E2F binding site upstream of the hTERT gene, thus preventing E2F from acting as a transcriptional repressor [17]. E7 has also been shown to interact with BRCA1, which acts as a repressor of the Myc-driven transcription on the E-Box of hTERT promoter [43]. This interaction leads to an upregulation of hTERT transcription. Furthermore, the implication of E7 in the prevention of immune response has been demonstrated. Indeed, E7 can interact with IRF-1 and inhibit its transcriptional activity, probably through the recruitment of HDACs [44].

Recently, E7 mediated-activation of three members of the Src family cytoplasmic tyrosine kinase (SFK), namely Src, Fyn and Yes, through phosphorylation was discovered [45]. It is interesting from a carcinogenesis point of view since this family of kinases is frequently upregulated, both transcriptionally and through their over-activation, in many cancer cells. Similar to E6, many additional known interaction partners for E7 have been identified and have been reviewed previously [46].

Finally, it should be mentioned that the HPV E5 protein has also been shown to possess potential interesting properties regarding transformation. Indeed, E5 interacts with the epidermal growth factor receptor (EGFR), the vacuolar ATPase, and affects communication between cells and expression of class I major histocompatibility complex (reviewed in [47]). However, despite these links to malignant progression, E5 is not expressed in most of HPV-positive cancers [2], which has led to the hypothesis that it might play a role only in the early events of transformation [48].

Hepatitis B virus

Hepatitis B virus (HBV) is one of the smallest human viruses; it possesses a partially double-stranded DNA genome and is one of the main causes of hepatocellular carcinoma (HCC). Latest studies estimate its implication in 50-55% of this type of cancer. Indeed, 80% of all HCC are attributable to an infection by HBV or hepatitis C Virus (HCV) [49, 50]. Although recent evidence indicates that

the HBV large surface antigen (LHBS) might be responsible for some carcinogenic effects [51], the HBx protein remains the key player in the development of HCC.

The precise mechanism by which HBx induces HCC is not known yet, but various results can explain its carcinogenic effects. It is essential to mention that in malignant HCC, HBx is usually integrated into the genome of infected cells [52]. An important role of HBx in tumor apparition is its capacity to interact with numerous signaling pathways involved in the balance between life and death of the cell. Indeed, HBx interacts with the important Pi3k/Akt pathway acting as an activator of Akt. When the latter is activated, there is inhibition of the transcriptional factor HNF4α responsible for cell differentiation of hepatocytes. The loss of HNF4α leads to a dedifferentiation of hepatocytes, and thus exacerbates cell proliferation [53]. In addition, HBx acts on the Wnt/β-catenin pathway by binding to APC (Adenomatous polyposis coli protein, a tumor suppressor protein) in a competitive manner to suppress β-catenin degradation mediated by GSK3 [54, 55]. β-catenin is then relocalized to the nucleus and activates the Wnt pathway which ultimately leads to cell transformation. HBx is also able to regulate β-catenin signalization by activating the Src proto-oncogene [56, 57]. Moreover, HBx regulates other important pathways like Jak/STAT [58], Notch1 [59], and Ras/MAPK [60].

Another role of HBx protein is modulating the expression of cellular genes using multiple different mechanisms. First, HBx is a transcriptional activator of many genes, mainly through protein-protein interactions with transcription factors [61, 62]. Transcription activation of NF-κB, AP-1 and survivin [63] by HBx leads to increased expression level of oncogenes such as c-myc [64, 65]. HBx also achieves enhanced gene expression by upregulating transcription factors, such as RNA Polymerase II transcription factors like AP-1, AP-2 [66], NF-κB, and transcription factors of RNA polymerase III [67]. HBx also plays a major role in the modulation of non-coding RNAs, such as lncRNA and miRNA. For example, miR-205 and mir-15b are downregulated while HULC (highly upregulated in liver cancer), miR-21 and miR-224 are upregulated in HCC. More examples of non-coding RNAs modulated by HBx are known and have been reviewed elsewhere [68]. Finally, HBx protein is also implicated in epigenetic modifications [69]. Amongst other, HBx activates the methyltransferase activity which is involved in abnormal methylation of CpG islets in various genes implicated in tumor suppression [70-72]. HBx can also induce histone acetylation in genes involved in tumor development [73].

Like the HPV E6 protein, the HBV Hbx protein is able to interact with p53 by binding to its C-terminus, thus inhibiting its activity [74]. However, a recent study showed that HBx is not completely inhibiting p53, but rather re-wiring it to enhance the expression of proliferation genes and lower the expression of cell death genes [75]. HBx can also act on cell survival, by downregulating pro-apoptotic factors implicated in tumorigenesis such as PDCD4 factor (programmed cell death 4) and PTEN [76]. The HBx protein can also promote invasion, by activating COX-2 which leads to activation of MMP-2, a metalloproteinase involved in metastasis [77]. Finally, the HBx protein also stimulates proliferation of quiescent cells through dysregulation of cell cycle checkpoints, for example by activating the Ras pathway as mentioned before [78].

In addition to HBx, other HBV proteins, such as L and M which share the preS2 domain, show increasing evidence that they might play a role in HCC development. The role of the preS2 domain in cancer is more recent, so less information is available about its oncogenic potential. What is currently known is that L and M can acquire their oncogenic potential through a mutant form of preS2. This mutant domain can play a role at the transcriptional level in increasing the activity of telomerase through its interaction with the hTERT promoter [79]. Furthermore, the preS2 domain accumulates on the endoplasmic reticulum (ER) and therefore causes ER stress. This stress is dependent on the VEGF/Akt [80] and NF-κB/Cox2 [81] pathways, and there is also inactivation of pRB which activates the cellular cycle. All of this leads to a proliferative advantage of infected cells. DNA damage and genomic instability are then created [82], in addition to centrosome instability. The co-expression of mutant preS2 domain and HBx seems to have more effects in tumorigenesis and apparition of cancer in mice [83] compared to expression of either preS2 or HBx, hence showing the synergetic potential of viral oncoproteins.

Merkel cell polyomavirus

The Merkel Cell Polyomavirus (MCPyV), discovered in 2008, is a small dsDNA virus and it is the only polyomavirus that causes cancer in humans. MCPyV is present in up to 80% of cases of Merkel Cell Carcinomas (MCCs) [84]. In MCPyV-positive MCCs, the viral DNA is integrated into the host cell's DNA. The integration event induces a signature for large tumor antigen (LT-Ag) disruption in a specific region that prematurely truncates this viral protein. In addition, integration of viral DNA into the cell's genome involves a mutational disruption of the PTPRG gene which is a human tumor suppressor [84]. Despite this interruption, the differential splicing of the early mRNA produces large tumor antigen (LT-Ag) and small tumor antigen (ST-Ag) in MCCs [85]. Conservation between MCPyV LT-Ag and its well-known homolog LT-Ag from simian virus 40 (SV40) has allowed numerous inferences in regard to cellular interacting partners for LT-Ag.

Truncation of the LT-Ag C-terminus implies the loss of the helicase and DNA binding domain [84, 85]. The LT-Ag ability to support viral replication is therefore inhibited; the viral lytic replication that could be fatal to the cancer cells is therefore abrogated [85, 86]. The C-terminus of the truncated LT-Ag contains an LXCXE motif which allows binding to the Rb protein (pRb) and its subsequent inactivation [84, 85, 87, 88]. As previously discussed, pRb is a critical factor in cell cycle control [89]. Thereby, Rb regulates entry into the S phase but, when it is bound to LT-Ag, this S-phase checkpoint is bypassed, and cells proliferate [90]. LT-Ag has an N-terminal J-Domain which interacts with heat-shock protein 70 family (Hsp70s), specifically with Hsc70 [91, 92]. This interaction stimulates Hsc70 ATPase activity and allows the release of E2F from its complex with Rb protein family members (p130-E2F and p107-E2F complexes only) [93-95]. LT-Ag also allows immune evasion by downregulating the expression of Toll-like receptor 9 (TLR9) which is a receptor of viral or bacterial dsRNA. Therefore, infected cells are liberated from host innate immune surveillance [96].

MCPyV has two unique regions that differentiate it from other polyomaviruses: MCPyV Unique Region 1 and 2 (MUR1 and MUR2). These regions are not necessary for the development of MCCs, but MUR1 allows higher expression levels of LT-Ag in MCCs [92]. It was also shown that MUR1 binds to hVam6p, a cellular protein involved in lysosomal trafficking [97]. This interaction with LT-Ag results in the translocation of hVam6p from the cytoplasm to the nucleus and inhibits lysosome clustering. However, the role of hVam6p in MCCs is still unclear [92]. The role of MUR2 is not known and is not expressed in MCCs due to the truncation of LT-Ag.

The other viral protein involved in MCPyV carcinogenesis is the small tumor antigen (ST-Ag). The N-terminus of this viral protein shares similarities with LT-Ag including the J Domain which interacts with Hsc70. Like LT-Ag, ST-Ag allows immune evasion by downregulating the expression of the same member of the Toll-Like Receptor family as LT-Ag, TLR9 [96]. Also, ST-Ag disturbs the cap-dependent translation by targeting the initiation factor 4E binding protein 1 (4E BP1) and hyperphosphorylating it. As a result, eukaryotic translation initiation factor 4E (eIF4E) is released from the 4E-BP1-eIF4E complex and promotes cell growth by higher translation levels [98]. ST-Ag also interferes with proteasomal degradation *via* its large T-antigen stabilization domain (LSD) in C-terminus, which binds to E3 ubiquitin ligase SCFFbw7. This allows stabilization of E3 ubiquitin ligase Fbw7 targets, such as the other viral oncoprotein, LT-Ag, and cellular oncogenes like c-myc and cyclin-E [99]. However, the ability of ST-Ag to transform cells is still controversial. Shuda, M. *et al*. have also shown that ST-Ag transforms rodent fibroblasts independently of LT-Ag and that the knockdown of ST-Ag leads to growth arrest of MCC cells [98, 100]. However, another group of researchers has found that ST-Ag is dispensable for growth of cells [101]. Further studies will surely explain more precisely the transforming potential of ST-Ag, but available evidences clearly show its involvement in MCPyV-mediated transformation.

Epstein-Barr virus

Epstein-Barr virus (EBV) or Human Herpesvirus 4 (HHV4) was discovered in cultured Burkitt's lymphoma cell in 1964 [102] and belongs to the Herpesviridae family. It has a 172kb linear double-stranded DNA genome and mainly infects B cells and epithelial cells. Three different types of latency

exist for this virus and differ greatly regarding viral genes which are expressed. EBV-associated malignancies include Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma, and gastric carcinoma [103]. Viral oncogenicity is conferred by both nuclear antigens (EBNA-1 and EBNA-2), LMP2, and BARF1.

The role of EBNA-1 protein in EBV carcinogenesis is important, as it is the only viral protein expressed in all types of latency, as well as in all EBV-positive tumors [104]. However, research has only recently begun to undercover its implication in tumorigenesis. First, EBNA-1 modulates pathways involved in cell proliferation. It upregulates STAT-1 and downregulates TGF-β signaling pathway [105]. It also inhibits the NF-κB pathway by preventing the phosphorylation of IKKα/β [106]. EBNA-1 also prevent apoptosis through a p53-dependant pathway, by binding to UPS7 which lowers the p53 levels [107]. Moreover, EBNA-1 also decreases the levels of PML and PML nuclear bodies which results in reduced levels of p53, thereby promoting cell survival in gastric carcinomas [108, 109]. Furthermore, EBNA-1 also promotes DNA damage, genomic instability and ROS production through the upregulation of the catalytic subunit of the leukocyte NADPH oxidase, NOX2/gp91^{phox} [110].

The EBV EBNA-2 protein seems to be essential for transformation of B-cells *in vitro* [111], but its expression may be less important for malignant growth *in vivo* because it is only expressed in tumors of immunocompromised patients [111, 112]. Interestingly, EBNA-2 is a functional homolog of Notch and its presence leads to expression of a subset of shared targets [113]. Interaction between EBNA-2 and EBNA-LP is able to induce G0 - G1 cellular transition, thus promoting cell growth [114].

The EBV latent membrane protein 1 (LMP1) is a membrane protein that acts as the CD40 receptor on the cell surface [115]. It can recruit tumor necrosis factor receptor (TNF-R)-associated factors (TRAFs), leading to signaling through the NF-κB pathway [116]. The CD40 receptor is important for survival of B cells [117], and the NF-κB pathway drives uncontrolled cell proliferation. Cell proliferation is further enhanced in B-cell by LMP1-dependent upregulation of IL-10 [118]. LMP1 also protects cells from apoptosis by increasing levels of inhibitors of apoptosis such as Bcl-2 and A20 [119, 120]. More than just a driver of cell growth, LMP1 promotes the malignant phenotype of the cell. ETS1, a transcription factor with oncogenic activity involved in invasion and metastasis, has induced expression in the presence of LMP1 [121]. Moreover, LMP1 triggers other important signaling pathways dysregulated in cancer, such as AP-1, JAK/STAT and PI-PLC-PKC [122]. Finally, LMP1 has been shown to drive cellular immortalization, through increased activity of the human telomerase catalytic subunit (hTERT) [123].

The EBV BARF1 protein is also latently expressed, and its structure consists of two immunoglobulin (Ig)-like domains [124]. The oncogenic potential of BARF1 is important since this protein induces transformation of rodent fibroblasts and immortilization of primary primate epithelial cells [125, 126]. Several studies showed the expression of BARF1 in the epithelium tissue of EBV-associated malignancies such as gastric carcinoma and nasopharyngeal carcinoma [127, 128]. In transfection assays, BARF1 protein is secreted into the culture medium and contribute to the increase in NPC (nasopharyngeal carcinoma) cell density [128]. Mainly, BARF1 modulates the host immune response to EBV infection by binding to colony-stimulating factor-1 (CSF-1), a pleiotropic cytokine, and by acting as its receptor [129]. It also activates cell cycle by both paracrine and autocrine ways [130, 131]. Finally, BARF1 has anti-apoptotic effects by directly activating the Bcl-2 anti-apoptotic protein [132, 133]. Interestingly, BARF1 has been shown to interact with hTid-1, which has implications in apoptosis, but the impact of this interaction has not been assessed [134].

Kaposi's sarcoma human virus

Kaposi's Sarcoma Human Virus (KSHV) or human herpesvirus-8 (HHV-8) is sub-classified as a gammaherpesvirus. The most common malignancy associated with this virus is Kaposi's sarcoma (KS) which is one of the most prevalent virally-induced cancers among HIV-infected patients [135, 136]. There are other malignancies associated with KSHV like primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) [137]. It is noteworthy that KSHV infection does not seem to lead to cancer in the absence of immunosuppression. Interestingly, KSHV encodes for a significant

number of cellular homologs, such as vGPCR, vCyclin, vFLIP, vBCL-2, vIL-6, vIRFs, and vCCLs. Since cellular homologs of these proteins are involved in cell signaling, cell cycle progression, apoptosis and immune response, the oncogenic implications of these virally encoded cellular proteins are likely. Other KSHV proteins with known oncogenic activity are LANA-1, Kaposin, K1 and K15.

LANA-1 is an oncogenic protein that plays an important role in KSHV-mediated carcinogenesis because of its constitutive expression in all latently infected KSHV cells [138]. Also, LANA-1 is a viral homolog of the previously discussed EBV protein EBNA-1. Mainly, this protein is involved in cell cycle regulation and apoptosis through its interaction with p53 and pRb. LANA-1 inhibits p53-induced apoptosis and is also able to repress its transcriptional activity [139]. On the other hand, LANA-1 interaction with pRb releases E2F transcription factor, leading to progression into the cell cycle [140]. LANA-1 also induces degradation of Bub1, one of the main spindle checkpoint proteins, by the ubiquitin-dependent pathway which results in increased chromosomal instability into the rapidly replicating cells [141]. Epigenetic modification in the TβRII promoter by LANA-1 inhibits signaling through the TGF-β pathway which could lead to apoptosis and growth inhibition [142]. Furthermore, LANA-1 can interact with the β-catenin pathway through the glycogen synthase kinase-3β (GSK-3β). Binding of LANA-1 to GSK-3β leads to its relocalization to the nucleus, where it is unable to phosphorylate β-catenin, thus relieving inhibition of this pathway and leading to upregulated levels of oncogenes such as Myc and Jun [143, 144]. Recently, the interaction of LANA-1 with Par3, an epithelial polarity regulator and overexpression of SNAIL, a protein implicated in epithelial-mesenchymal transition (EMT), positioned LANA-1 as a probable potentiator of EMT, which is an emerging hallmark of cancer [145, 146].

The KSHV K1 protein is encoded by the first open reading frame in the viral genome and has various roles in cellular signal transduction and viral lytic reactivation [147]. Its expression has been detected in different cancer types such as KS, PEL, and MCD, and transgenic mice expressing K1 develop more tumors [147], suggesting a probable role in carcinogenesis [148, 149]. Moreover, the expression of K1 in endothelial cells increases production and secretion of VEGF, blocks apoptosis, and activates Akt prosurvival signaling which leads to cell immortalization and transformation [148]. K1 is also able to act on other cellular pathways. For example, it constitutively activates the NF-κB pathway and enhances the expression of fibroblast growth factor (FGF) in mice [147]. Moreover, K1 upregulates the PI3K pathway and inhibits PTEN (phosphatase and tensin homolog, a tumor suppressor protein) in B lymphocytes, leading to inactivation of members of the forkhead transcription factor family (FKHR) implicated in cell cycle progression and apoptosis [150]. K1 also has more effects on apoptosis by blocking Fas-mediated apoptosis through its immunoreceptor tyrosine-based activation motif (ITAM). Association of K1 with Fas prevents further binding of FasL which blocks apoptosis [151, 152]. It is also known that K1 expression in lymphocytes activates Lyn and Syk kinase, the latter one being well studied in B-cell tumors [150, 153, 154]. Finally, it was demonstrated that K1 enhances angiogenesis in chick chorioallantoic membrane (CAM) and nude mice models [155, 156].

vCyclin, a viral homolog of cellular cyclin D, is a constitutive activator of cyclin-dependent kinase 6 (CDK6) [157]. The complex between vCyclin and CDK6 is resistant to CDK inhibitors $p16^{Ink4a}$, $p21^{Cip1}$, and $p27^{Kip1}$ leading to unrestricted progression into the G1/S transition [158]. The vCyclin-CDK6 complex can phosphorylate a larger range of substrates, such as pRb, $p27^{Kip1}$, and Cdc6 [159]. Additionally, studies showed that vCyclin has no effect on cell proliferation and cell cycle progression at a low-density proliferating state, but does at a high-density contact-inhibited state, which is crucial for tumor development [160]. However, vCyclin is more than a simple cell cycle regulator, being also involved in apoptosis and uncontrolled growth. STAT-3 inhibition of DNA-binding through vCyclin interaction relieves growth inhibitory signal coming from oncostatin M [161]. vCyclin also acts as an anti-apoptotic protein, being able to inactivate the pro-apoptotic protein Bcl-2 through phosphorylation together with CDK6 [162].

KSHV encodes a viral homolog of the FADD-like interferon-converting enzyme (FLICE) inhibitory protein (vFLIP). The KSHV vFlip (viral FLICE inhibitory protein) is a polypeptide characterized

by two tandem death effector domains (DEDs). This protein is homologous to the cellular FLIP protein and is able to inhibit apoptosis signaling coming from caspase-8. vFlip can be recruited to the DISC (Death-Inducing Signaling Complex), replacing procaspase 8 and preventing its interaction with the complex [163]. In addition, vFLIP can also inhibit FAS-mediated apoptosis [164]. However, many studies showed that vFlip is more than a latent gene with anti-apoptotic functions, being able to activate NF-κB pathway and help immune evasion [165, 166]. For example, activation of the NF-κB pathway in virus-positive PEL is crucial for cell proliferation, survival, and maintenance of the tumor phenotype [167, 168]. Moreover, expression of vFLIP also increases the level of COX-2 and its associated metabolite, PGE2, which are involved in inflammation, angiogenesis, and metastasis, through this pathway [169]. Finally, it is important to mention the significant role of vFlip in immune evasion. vFlip triggers a profound B-Cell germinal center suppression, hampering humoral immune response and abolishing T cell recognition of KSHV-infected cells *via* modifications to the microenvironment [170].

The KSHV vIL-6 protein is a homolog of cellular IL-6, with the same biological properties, such as promoting cell growth of IL-6-dependent cell lines [171]. Also, vIL-6 can stimulate cell survival and extrahepatic acute-phase response by activating several signaling pathways. One interesting difference between IL-6 and vIL-6 is that vIL-6 binds directly to the gp130 receptor subunit, even in the absence of the main IL-6 receptor, IL-6R [172]. This indicates that vIL-6 can stimulate multiple cell types that are not stimulated by IL-6 since its activity is not limited to cells that express IL-6R [173]. It is also known that vIL-6 can induce B cell proliferation and contribute to cell transformation. As a result, this viral protein plays a significant role in KSHV-related hematopoietic tumorigenesis [174]. In fact, it was determined that vIL-6 is expressed in 2-5% of PEL cells and 5-25% of B cells near follicular centers in multicentric Castleman's disease [175]. Interestingly, NIH3T3 cells expressing vIL-6 show increased angiogenesis [176]. This result corroborates other results obtained in CAM model wherein vIL-6 promotes angiogenesis and tumorigenesis in endothelial cells. One possible explanation might be the ability of vIL-6 to induce secretion of both cellular IL-6 and VEGF to promote cell proliferation. It should be noted that vIL-6 protein is also able to contribute to KSHV immune evasion by the inhibition of IFN-α-induced antiviral response [177].

KSHV encodes many more proteins that have known or potential implications in regard to carcinogenesis. vCCL1, vCCL2, and vCCL3 are cytokine homologs that have angiogenic roles and induce secretion of VEGF1 and trigger overexpression of its receptor, VEGFR1. Another KSHV protein, vGPCR, is similar to G protein–coupled receptors (GPCRs), and interacts with some of those virally encoded chemokines thereby triggering cell signaling in both ligand-dependent and ligand-independent fashions and modulating angiogenesis. vIRFs (1, 2 and 3) are interferon response factors that suppress transcription of IRF1 regulated genes, act as oncogenes (at least for vIRF1) and bind to p53 (vIRF1 and 3). Finally, K15 is also able to induce cell proliferation. The multiple roles of these viral oncogenes have been addressed in various reviews [159, 178].

Hepatitis C virus

HCV is a small single-stranded RNA virus belonging to the Filoviridae family. HCV is responsible for 25-30% of all HCC cases in the world [49]. There is not a single defined mechanism by which HCV could lead to cancer, but the major hypotheses involve the viral non-structural protein 5A (NS5A), the core protein, the early protein 2 (E2), and the non-structural protein 3 (NS3).

The HCV NS5A protein has a significant role in transformation mediated by HCV. Indeed, NS5A can enhance oxidative stress [179, 180] and dysregulate important pathways in the control of the cell cycle. Through increased endoplasmic reticulum (ER) stress, NS5A reduces the expression of PTEN at the transcriptional level. The production of ROS (reactive oxygen species) is consequently increased, activating NF-κB pathway and promoting Akt activation [181]. This leads to cell survival and protects cells against apoptosis. NS5A also constitutively activates STAT3, again through ER stress [179, 182], which leads to a proliferative phenotype. In addition, NS5A can bind to p53 and inhibit its transcriptional activity. For example, one of the impacts is the transcriptional dysregulation

of $p21^{Cip1}$, thus preventing cell cycle arrest in G1 state and apoptosis [183, 184]. Moreover, some data suggest that NS5A induces LTB expression (LTB is a member of the TNF-α family, and thus controls cell survival), which is known for its involvement in HCC induced by HCV [185].

The HCV core protein might be a candidate HCV protein involved in carcinogenesis because of its ability to transform mice cells [186]. Moreover, the HCV core protein cooperates with the Ras pathway in the transformation of cells [187, 188]. It can also activate the MAPK pathway and interact with many transcriptional factors such as LZIP [189], p21 [190, 191], DDX3 [192, 193] and NF-κB [194] directly or indirectly, which impacts the balance between death and cell survival. The core protein also activates the promoter of c-Myc, which is a potent proto-oncogene [195]. Although the core protein has been shown to induce carcinogenesis by inhibition of apoptosis, the results are still controversial. Indeed, some studies have demonstrated that the core protein might have apoptotic effects [196-198].

Aside from the roles of HCV NS5A and core protein, there is some other evidence that the HCV proteins NS3 and E2 could be involved in the apparition of cancer. Similar to NS5A, NS3 has been shown to sequester p53, thereby inhibiting p53-induced apoptosis [199]. Finally, E2 can inhibit apoptosis in cells by disturbing intrinsic apoptosis pathways and increasing proliferation in cells containing HCV replicons [200]. However, more evidence is needed to attribute the true carcinogenic role of these proteins.

Human T-cell Lymphotropic virus 1

Human T-cell Lymphotropic virus-1 (HTLV-1) is a retrovirus known to induce leukemia in infected T cells [201-203]. In fact, 2-5% of carriers will contract leukemia (ATL, adult T cell leukemia) more than 20 years after initial infection. HTLV-1 encodes numerous proteins, but it has been demonstrated that Tax-1 is the major protein responsible for its oncogenic effects. Tax-1 mainly induces mesenchymal tumors in mice [204] and its incorporation in cells leads to a proliferative response [205]. Tax-1 serves as a transcriptional activator and is responsible for the pathogenic effects of HTLV-1.

The primary mechanism by which Tax-1 acts on cellular effectors to favor tumorigenesis is by interfering with cellular transcription. Tax-1 regulates transcription through interaction with cellular transcription factors; Tax does not recognize specific DNA regions [206-208]. The presence of Tax-1 can modify the expression of numerous genes involved in cell survival. First, Tax-1 induces the expression of the Bcl-xL anti-apoptotic protein by activating NF-κB and CREB enhancer-binding proteins [209] which bind elements located in the Bcl-xL promoter [210]. On the other hand, Tax-1 can also repress pro-apoptotic genes. For example, Tax-1 inhibits Bax expression, and this repression is mediated by an E-box-containing element in the Bax promoter [211]. Furthermore, Tax-1 also negatively regulates proteins involved in DNA repair, such as the β-polymerase [212]. This allows an increased number of mutations in those cells. Tax-1 can also repress the expression of p53 in human cells. Two mechanisms can explain this repression: Tax can activate c-myc [213, 214] or NF-κB [214] in an Akt-dependent manner [215]. The activity of Tax-1 on NF-κB has been demonstrated to be dependent on the NF-κB protein complex p50 subunit activation and inhibition of IκB (activation of IKK). Activation of NF-κB indeed leads to a gene expression pattern responsible for increased proliferation of T-cells [216-219]. These genes include IL-2, IL-2Rα, c-fos, and CD40 [220-225]. Tax-1 activation of NF-κB is also dependent on Akt activation [215]. It should be noted that Tax-1 is also involved in cell cycle progression in two different ways. First, it leads to hyperphosphorylation of pRB [226] and also enhances its degradation by the proteasome [227]. Second, Tax-1 can downregulate Cyclin-dependent kinase inhibitor protein (CKI) at the transcriptional level [228, 229].

An RNA region in the 3' LTR of the HTLV-1 genome, named Hbz was thought to have some effects on maintaining transformed state of T-cells infected by HTLV-1 because most ATL cells still carry Hbz RNA and its encoded protein, HBZ [230]. HBZ protein has been known to play a crucial role in evading the immune system [231, 232], but recently some evidence showed that the HBZ protein can also activate abnormal proliferation of T-cell lymphocytes [233-235],

and inhibit apoptosis [232, 236]. Proliferation and invasion of cells mediated by HBZ occur by dysregulation of the Wnt pathway [235]. The expression of HBz also leads to cellular immortalization by increasing the levels of hTERT transcription [237, 238].

Another protein of HTLV-1, p12, helps in transforming cells by inducing activation of the Jak/STAT pathway through activation of IL-2R. It also increases STAT5 transcriptional activity, which is responsible for increased proliferation. Therefore, p12 induces a proliferative state independent of IL-2 [239]. Moreover, some studies demonstrated that the viral p30 protein is necessary for the complete transformation of cells infected by HTLV-1 [240]. The p30 protein was shown to dysregulate proliferation and cell cycle progression through c-myc, but the regulation of apoptotic genes by HTLV-1 remains to be fully investigated [241].

CONCLUSION

Viral infection is an important etiological factor for cancer development, accounting for nearly 20% of all cancers worldwide. In order to drive the transformation process, the seven well-known oncogenic viruses rely on viral proteins that act similar to cellular oncogenes. These viral oncoproteins modulate the signaling of multiple cellular pathways and have a broad diversity of interacting partners. Some pathways, such as the NF-κB pathway, and some cellular proteins, such as p53 and pRB, are key targets of numerous viral oncoproteins, thus underscoring their central role in the balance between normal and transformed phenotypes. Although this review mainly focused on the oncogenic roles of viral proteins, it is important to remember that the oncogenic activities of viral proteins are clearly not the only factor implicated in viral carcinogenesis. In addition to viral proteins, some viruses also encode functional RNA, such as long non-coding RNAs (lncRNA) and miRNAs that might be able to drive the development of cancers. EBV lncRNA EBER1 and 2 and EBV and KSHV miRNA, such as miR-BART5 and miR-K5 for example, are non-protein factors with potential implication in this process (reviewed in [242]). Moreover, chronic inflammation due to the immune response to infected cells is also an important factor for the development of chromosomal instability and acquisition of potentially oncogenic mutations (reviewed in [243]). However, most research in the field of virus tumors has focused on viral oncoproteins, since they present the greatest potential in clinical use as targets to prevent and/or cure cancer as well as being potentially utilized as biomarkers to monitor the stage and progression of tumors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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