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More than just oncogenes: mechanisms of tumorigenesis by human viruses

Marta M. Gaglia¹ and Karl Munger²

¹Department of Molecular Biology and Microbiology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

²Department of Developmental, Molecular and Chemical Biology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA

Abstract

Most humans are infected with at least one of the known human cancer viruses during their lifetimes. While the initial infection with these viruses does not cause major disease, infected cells can acquire cancer hallmarks, particularly upon immunosuppression or exposure to co-carcinogenic stimuli. Even though cancer formation represents a rare outcome of a viral infection, approximately one out of eight human cancers has a viral etiology. Viral cancers present unique opportunities for prophylaxis, diagnosis, and therapy, as demonstrated by the success of HBV and HPV vaccines and HCV antivirals in decreasing the incidence of tumors that are caused by these viruses. Here we review common characteristics and mechanisms of action of the human oncogenic viruses.

Introduction

The potential for an infectious etiology of carcinogenesis was first established in the early 1900's, when it was discovered that some cancers in animals could be transmitted by cell-free filtrates. Several decades of research revealed that these tumors were transmitted by retroviruses and that retroviruses triggered cancer by insertional mutagenesis or by expression of viral versions of cellular genes, later dubbed oncogenes. Evidence that some human cancers are caused by viral infections started to emerge in 1964, when Epstein and Barr discovered viral particles in Burkitt's lymphomas [1]. In 1970, virus-like particles ("Dane particles"), which are now known to be hepatitis B virus (HBV) virions, were detected in the blood of patients with infectious hepatitis [2]. In 1978, Stefania Jablonska and Gerard Orth reported the isolation of the human β -genus papillomavirus type 5 (HPV5) from a cutaneous squamous cell carcinoma [3], and in 1983 Harald zur Hausen's group isolated a different HPV, the α -genus HPV16, from a cervical carcinoma [4]. There are now several well-established human tumor viruses, which include approximately 12 "high-risk" α -HPVs, HBV, Hepatitis C virus (HCV), Epstein-Barr virus (EBV; a.k.a human herpesvirus

Correspondence to: Marta M. Gaglia (marta.gaglia@tufts.edu), or Karl Munger (karl.munger@tufts.edu).

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4 - HHV4), Kaposi's sarcoma-associated herpesvirus (KSHV; a.k.a. human herpesvirus 8 - HHV8), Merkel cell polyomavirus (MCPyV; a.k.a. human polyomavirus 5), and the human T-cell lymphotropic virus type 1 (a.k.a. human T-cell leukemia virus type 1 ; HTLV-1) [5] (Table 1). In addition, some β -HPVs cause cutaneous squamous cell carcinomas in patients with the rare hereditary skin disorder epidermodysplasia verruciformis and in long-term immunosuppressed individuals, for example organ transplant recipients [6,7]. Overall, viral infections contribute to at least 12% of all human cancers. Virus-associated cancers occur more frequently in individuals with a compromised immune system, or those living in poor sanitary conditions with limited access to healthcare. In fact, the high incidence of cancer in immunosuppressed patients was a key characteristic that led to the finding that Kaposi's sarcoma, caused by KSHV, and Merkel cell carcinoma, caused by MCPyV, were virus-induced tumors [8,9].

There are at least three mechanisms by which viral infections can contribute to oncogenesis: (1) viruses can encode viral proteins that are oncogenic, (2) they can cause chronic inflammation and/or (3) promote genomic instability or other host cell alterations that lead to carcinogenesis. In this short review we will point to shared features of different human cancer viruses and how these relate to their mechanisms of oncogenesis. Moreover, we will discuss the emerging model that some viruses may contribute to initiating cancer formation, but may not be required for tumor maintenance, similar to non-viral carcinogens. In these cases, the viruses and viral proteins may only be detectable in pre-cancerous lesions, but not in the tumors. Such "hit-and-run" mechanisms are notoriously difficult to definitively prove but could be a major mechanism by which viruses may contribute to many types of cancers.

Oncogenic viruses are species-specific

An interesting characteristic of human cancer viruses is that they are species-specific. None of them can productively infect mice and in most cases not even non-human primates. From an experimental standpoint, this means that the majority of the mechanistic insights on oncogenesis have been derived from experiments with tissue culture cells and with transgenic animals overexpressing oncogenic viral proteins. Many approaches have been and continue to be explored to generate animal models for human cancer viruses, but only very few exist in animals that can be modified genetically. Humanized mouse models are sometimes used, for example for HBV and HCV, but they are usually immunosuppressed, and cannot be used to study interactions with the immune system for clearance and oncogenesis [10,11].

For some viruses, related rodent viruses are used to study the dynamics of infection *in vivo*, although not all aspects of pathogenesis are faithfully modeled in these viral infections. The best-known example is the murine polyomavirus which, depending on the genetic background of the infected mouse, can trigger formation of cancers in a variety of tissues, as the name "polyoma" implies. However, the only oncogenic human polyomavirus, MCPyV, is only distantly related to the murine polyomavirus. Moreover, the major oncogenic activity of the murine polyomavirus is encoded by the middle T antigen, but MCPyV does not encode a middle T protein. Hence, while studies with murine polyomavirus have provided important insights into human carcinogenesis [12], this virus is not an appropriate animal

model for MCPyV-mediated human carcinogenesis. For γ -herpesviruses, the murine herpesvirus 68 (MHV-68) is used to study acute infection *in vivo*, virus dissemination and development of latency [13]. Formation of tumors with this virus occurs in a minority of cases and only after nine months of infection, unless the infected mice are immunosuppressed due to genetic mutations or drug treatment [14]. While this is analogous to disease in patients, this model is not easily amenable to genetic study. γ -herpesviruses that infect non-human primates also exist and have revealed important insights into mechanisms of transmission, viral latency, reactivation and immune responses [15,16]. More recently a papillomavirus that infects mice, MmuPV1, has been discovered and is actively being developed as a model of HPV infection [17–19]. MmuPV1 is phylogenetically most related to the cutaneous β - and γ -HPVs and its oncogenic E6 and E7 proteins have biological and biochemical activities that resemble those of β - and γ -HPVs [20–22]. Experimental MmuPV1 infections cause cutaneous papillomas that, similar to β -HPV induced lesions, can progress to cutaneous squamous cell carcinomas upon UV exposure [23]. In the case of HBV, duck and wood-chuck hepadnaviruses are used in their natural hosts as models of HBV replication and pathogenesis, but, like the mouse polyoma, herpes and papillomaviruses, they do not replicate all features of human HBV infection [24].

From a biological perspective, it is interesting to speculate that, unlike acute infections, the kind of virus-cell interactions that give rise to cellular transformation are exquisitely tuned to the specific host organisms and even to a specific cell type. For example, there are many core genes that are shared between human and rodent γ -herpesviruses, but many of the factors that contribute to transformation are unique to the individual viruses or highly divergent in MHV68 (for example, LMP1 in EBV, vFLIP and LANA in KSHV, and the micro RNAs in both viruses) [25,26].

The pronounced species specificity of the human cancer viruses has made it very hard to conclusively prove a viral etiology for a given cancer, and the mere detection of viral sequences in a tumor is not sufficient to prove causation [27]. However, several decades of intensive investigation by clinicians, population scientists and basic scientists have now generated compelling evidence for a viral etiology of specific human cancers. In the case of HBV and HPV, the ultimate proof was provided by the widespread use of prophylactic vaccines that have had a dramatic impact on the incidence of HBV-associated hepatitis and hepatocellular cancers [28] and HPV-associated high-grade cervical intraepithelial neoplasia, a necessary precursor of cervical cancer [29].

Modalities of viral oncogenesis

Tumor cells differ from normal cells by several characteristics that Hanahan and Weinberg have dubbed the “hallmarks of cancer”. Originally, these included sustained proliferation and replicative immortality, resistance to cell death and growth inhibition, angiogenesis and metastatic behavior [30]. More recently, it was recognized that deregulation of metabolism, avoidance of immune responses, stimulation of pro-tumorigenic inflammation and genomic instability are also key elements of the cancer phenotype [31]. Inflammation and genomic instability are considered “enabling characteristics”, because they also contribute to cancer development and progression [31]. In non-viral cancers, tumor cells acquire these hallmarks

as a consequence of oncogene activation and tumor suppressor inactivation, as well as paracrine effects of the stroma. Similarly, human tumor viruses affect the hallmarks of cancer by encoding oncogenic proteins, and/or by triggering enabling characteristics like inflammation and other changes to the microenvironment, as well as genomic instability that accelerate cancer formation (Figure 1) [32].

Papilloma- and polyomaviruses are classical examples of human cancer viruses that encode oncogenic proteins (Figure 1). The MCPyV tumor antigens (small T and large T) and the HPV E6/E7 oncoproteins have no close cellular homologues and contribute to carcinogenesis by driving the degradation and inactivation of the cellular p53 and retinoblastoma (RB1) tumor suppressors, respectively, and impinging on many other tumor suppressive and oncogenic pathways including Notch and TGF β signaling [33–36]. EBV and KSHV also encode several proteins that contribute to oncogenesis. In EBV these include the Epstein Barr nuclear antigen proteins (EBNAs) and the latent membrane proteins (LMP1 and 2), and in KSHV the latent nuclear antigen (LANA), and the signaling proteins vGPCR, K1, K15, kaposin B, vCyclin and vFLIP [37–47]. These KSHV and EBV proteins up-regulate expression of oncogenic cellular proteins and microRNAs, down-regulate tumor suppressor expression and activate signaling pathways, like the NF- κ B pathway, that promote growth and proliferation of B cells and endothelial cells, the cells that give rise to EBV- and KSHV-induced tumors [48]. Interestingly, several of the KSHV oncoproteins are viral counterparts of host proteins with functions in cell proliferation and apoptosis regulation. In addition, KSHV- and EBV-encoded microRNAs and the EBV-encoded small RNAs EBERs also regulate angiogenesis, cell proliferation and apoptotic pathways [49,50]. Tumors caused by viral oncogenes are often “addicted” to the expression of these proteins, i.e. they do not survive or grow without them, much like non-viral cancers can be addicted to specific oncogenic pathways [51]. Indeed, experiments performed with MCPyV and HPV positive cancer cell lines and transgenic mouse models suggests that inactivation of the viral oncogenic proteins will cause regression of the tumors [52]. In keeping with this idea, comparative genomic analyses of MCPyV-positive and negative Merkel cell carcinomas and HPV-positive and negative head and neck cancers have shown that virus-induced tumors on average carry fewer cellular mutations than the virus negative cases [53–57]. Interestingly, the mutations in non-viral tumors activate or inactivate the very same pathways that the viral oncogenic proteins attack, indicating that the etiology of the tumors is ultimately analogous [53–57].

In contrast to this classical oncogene-based transformation paradigm, HBV and HCV are thought to cause tumorigenesis predominantly by inducing a chronic inflammatory state (Figure 1). In HCV infection in particular, hepatocellular carcinoma generally arises after a stage of fibrosis and cirrhosis of the liver, which supports a key role of inflammation for the oncogenesis process [58,59]. Several different aspects of inflammation may contribute to the development of these tumors. Chronic HBV and HCV infections stimulate an immune response that kills hepatocytes, followed by liver regeneration. If the infection is not cleared, the damage and regeneration cycles occur repeatedly, which promotes the accumulation of oncogenic mutations and epigenetic changes that lead to tumorigenesis. In addition, inflammatory and immune responses lead to increased production of reactive oxygen species (ROS) and nitrogen reactive species that induce mutations and can thus promote oncogenic

transformation of hepatocytes [60,61]. Although the chronic response to infection is likely the main contributor to hepatocellular carcinoma development, viral protein expression may also play a direct role in tumorigenesis. In HBV, the X protein (HBx) has been reported to have oncogenic activity [62]. While no clear oncogenic role has been reported for HCV proteins, the core protein and several non-structural HCV proteins activate signaling pathways that contribute to HCV pathogenesis and could ultimately promote tumorigenesis [61]. However, these reports are based on overexpression studies, and how these findings may integrate in the process of tumorigenesis *in vivo* remains unclear.

Oncogenic herpesviruses also drive tumorigenesis by a combination of oncoprotein expression and inducing alterations to the tumor microenvironment (Figure 1). Indeed, while several KSHV proteins and the microRNA have oncogenic activities, Kaposi's sarcoma is considered a "paracrine neoplasia", and requires angiogenic and pro-survival paracrine factors for tumor initiation and maintenance [63]. EBV, KSHV and HPVs can also cause alterations in the cargoes carried by exosomes and other extracellular vesicles that are secreted by cells, thereby altering extracellular signaling, gene expression and biological properties of the tumor microenvironment [64–66]. Extracellular vesicles from HCV infected patients also contain HCV genomes and can transmit HCV infection thereby bypassing normal receptor mediated entry processes [67].

Another common contributor to tumorigenesis in all these infections is the development of genomic instability, which accelerates cancer development. Oncogene expression, changes to the cellular microenvironment, induced hyperproliferation, and ROS and other reactive species all drive genomic instability (Figure 1). In the case of the T cell leukemia-causing retrovirus HTLV-1, genomic instability may be the key factor in disease development, because the risk of leukemia development appears proportional to the number of cell divisions [68]. The increased T cell proliferation in infected cells and inhibition of DNA repair pathways by the HTLV-1 Tax protein both contribute to genomic instability and the accumulation of oncogenic mutations [68,69]. In addition, since HTLV-1 is a retrovirus that becomes integrated into the host cell genome as part of its normal life cycle, insertional mutagenesis may also cause oncogenic mutations [68,69]. Insertional mutagenesis may also contribute to HBV-induced hepatocellular carcinomas, as the HBV genome is consistently found inserted into cellular DNA in these tumors [61]. Indeed, genomic instability and HBx activity may cause some tumors through a classical oncogene-based mechanism, and this may explain why not all cases of HBV-associated hepatocellular carcinoma are preceded by cirrhosis or fibrosis, in contrast to HCV-related hepatocellular carcinoma [70].

Another source of DNA mutations are cytidine deaminases of the family of apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3 (APOBEC3), which are induced as a cell-intrinsic response to infection. APOBEC3 enzymes convert cytosines to uracils, thereby causing C to T, C to G and more rarely C to A mutations. Cells induce APOBEC3 expression to mutate and inactivate the invading viral genomes. However, these enzymes also generate collateral damage in the form of point mutations in the cellular genome that can drive cancer formation [71]. Consistent with this idea, a significant proportion of cellular mutations in HPV-associated cancers have an APOBEC3 mutational signature [72–74].

Even the process of viral genome replication *per se* can pose a risk for cancer formation. Several human tumor viruses, including KSHV, EBV, MCPyV and HPVs replicate their genomes at or near sites where genomic double strand DNA breaks are repaired. This strategy guarantees the availability of nucleotide pools and DNA polymerases that can be appropriated for viral genome replication. Therefore, these viruses deliberately stimulate the generation of double strand DNA breaks, presumably to provide for sites of genome replication [75]. This can cause an increase in genomic aberrations, most notably chromosomal translocations, as a result of breakage-fusion-bridge cycles. HPV E6 and E7, HTLV-1 Tax and the HBx protein also induce a variety of mitotic abnormalities that can cause chromosome missegregation and aneuploidy, the most prevalent manifestation of genomic instability in human solid tumors. For example, HPV E7 proteins induce aberrant synthesis of mitotic spindle pole bodies, which cause formation of multipolar mitoses, a well-known hallmark of HPV-associated premalignant lesions and cancers [76].

The connection between persistent infection and oncogenesis

There are two different replication strategies that viruses commonly use. The first is to quickly take over and reprogram the cell and produce as much viral progeny as possible to be able to re-infect the next host. In its most extreme form, such a strategy is untenable evolutionarily, since it would eventually cause the total elimination of the host population. This problem is tempered by the fact that these viruses are usually cleared by the host's immune system, and thus result in severe disease and death in only a subset of the population. The second strategy is for a virus to establish a long-term persistent infection. Long-term infection necessitates effective evasion of innate and adaptive immune responses of the host for extended periods of time. It also requires the ability for the viral genomes to persist. Because virus-associated cancers arise years or decades after the initial infection, it is not surprising that this second type of "lifestyle" is commonly associated with oncogenic viruses (Figure 1). In addition, acute infections are usually highly cytopathic, which is incompatible with long-term transformation of infected cells. The classical example of a persistent infection are herpesviruses, which can deposit their genomes in latently infected cells, and periodically reactivate to spread to new hosts. HPVs, HBV, HCV, HTLV-1 and MCPyV also establish persistent infections, but unlike EBV and KSHV they do not go dormant. Instead they continue to replicate their genomes, presumably at low levels, and to produce progeny virus without dramatic cytopathic effects. An extreme version of viral persistence are non-productive infections, i.e. situations where viral proteins are synthesized but no infectious viral progeny is produced. Non-productive infections can arise as a consequence of accidental and irreversible integration of portions of the viral genome into a host chromosome, aberrations in epigenetic modifications and/or mutations of the viral genome, or infection of a cell type that does not support the viral life cycle. Such non-productive infections often irreversibly terminate the viral life cycle and are key for tumorigenesis for HPVs and MCPyV. The majority of HPV-associated cervical cancers contain integrated HPV sequences, with consistent expression of the viral HPV E6 and E7 genes [77]. Similarly, MCPyV-associated Merkel cell carcinomas consistently express integrated viral genome fragments that drive expression of the small tumor antigen (Small T) and truncated versions of the large tumor antigen (Large T) [8].

There are several ways in which the demands and consequences of latent, persistent or non-productive infections dovetail with oncogenic processes and the induction of cancer hallmarks. First, the infected cells need to survive in order for the viruses to persist, which necessitates resistance to apoptotic stimuli and increased proliferative capacity (Figure 1). Indeed, many of the aforementioned γ -herpesvirus oncoproteins and non-coding RNAs are produced during latency, when only a small subset (at most 10%) of herpesviral genes are expressed. In addition, γ -herpesviruses and HPVs are known to extensively remodel the metabolic profile of infected cells, presumably to provide resources for the increased proliferation. These changes resemble the canonical Warburg effect discovered in non-viral cancers, which consists of a metabolic switch to glycolysis rather than the electron transport chain for ATP generation [78–80]. These metabolic changes support the increased proliferative capacity of the cells but could also be ultimately exploited for development of new drug targets.

In the case of HPVs, the need for continued proliferation is due to the fact that, while HPVs replicate in terminally differentiated cells, they require cellular machinery and nucleotide pools for viral DNA replication. To solve this problem, high-risk HPVs use E7 to uncouple differentiation from cell cycle withdrawal, i.e. to keep infected epithelial cells in a replication-competent state while they are differentiating. Not surprisingly, this behavior, as well as expression of the E7 oncogene, are sensed as abnormal, and the cell responds by triggering apoptosis and oncogene-induced senescence [81,82]. In fact, the high-risk HPVs have evolved to target p53 and RB1 and thus cause cancer hallmarks because p53 and RB1 are key mediators of apoptosis and senescence [83].

In addition to direct carcinogenic effects, the continued replication and survival of cells infected with oncogenic viruses also potentiates the effects of the virus-induced genomic instability (reviewed above). This is because the compromised cellular checkpoint activity enables the survival of mutated cells and propagation of genomic instability. It is important to note that in all cases, the purpose of activating oncogenic processes is not cellular transformation but promoting the viral infection. Thus, the emerging view is that viral carcinogenesis represents a rare and accidental consequence of a viral infection.

Cases in which viral replication is required for oncogenesis

Whereas non-productive infections are typically detected in HPV- and MCPyV-associated cancers, active lytic infections are thought to promote tumorigenesis in γ -herpesvirus (KSHV and EBV) associated cancers. KSHV latent infection of lymphatic endothelial cells causes de-differentiation, expression of blood endothelial cell markers, and their conversion into morphologically altered “spindle cells” [63]. While these latently infected spindle cells constitute the majority of Kaposi’s sarcoma lesions, it has long been known that virus replication occurs in a small percentage of Kaposi’s sarcoma cells. Several observations support the model that these lytically replicating cells are important for the development of tumors. For example, inhibiting viral replication by treating Kaposi’s sarcoma patients with antiviral drugs has been reported to reduce tumor development in some studies [84–87]. One study reported that antiherpesviral drugs also helped the remission of a patient with primary effusion lymphoma, also caused by KSHV [87]. Moreover, cohort studies have shown that

Kaposi's sarcoma patients harbor antibodies against KSHV lytic proteins prior to disease onset [88]. The B cell version of multicentric Castleman's disease is a KSHV-associated lymphoproliferative neoplasm that is also characterized by lytic KSHV replication [89]. The role of lytic replication is not as well established for EBV-related tumors, but reports have been emerging describing the presence of lytic EBV cells in EBV tumors, and the oncogenic functions of EBV lytic proteins [90,91]. The contribution of lytic replication in EBV infection has been more extensively explored in connection with nasopharyngeal carcinoma. Similar to Kaposi's sarcoma cases, lytic protein antibodies are detected in patients with nasopharyngeal carcinoma [92]. Moreover, a large-scale prospective study in Taiwan showed that patients that had antibodies to at least one of two lytic proteins were at least four times more likely to develop nasopharyngeal carcinoma than seronegative patients [93]. Direct evidence of the importance of lytic reactivation in EBV tumors was recently provided by a study examining a naturally occurring polymorphism in the promoter of the EBV BZLF1 protein, which controls the latent-to-lytic switch of the virus [94]. This polymorphism is over-represented in the EBV sequences isolated from tumor tissues of patients with EBV-associated nasopharyngeal carcinoma, AIDS-associated lymphomas, Burkitt's lymphomas and gastric carcinomas [94]. Interestingly, this cancer-associated polymorphism leads to increased BZLF1 expression in response to reactivation stimuli such as B cell receptor activation and, consequently, increased lytic reactivation [94]. The over-representation of this polymorphism in tumors suggests that increased lytic reactivation promotes tumor development.

In KSHV and EBV, the potential contributions of the lytic cycle are twofold. On one hand, lytically infected cells may provide secreted paracrine factors that promote tumor formation, cell survival, and, in the case of KSHV, angiogenesis. In particular, several KSHV-encoded signaling molecules and cytokine homologs expressed during lytic replication participate in the oncogenic process through paracrine signaling [63]. Also, lytic proteins may contribute to carcinogenesis by activating cellular oncogenic pathways or by promoting genetic instability. In this case, an abortive or non-cytopathic infection may have to occur for these changes to result in cellular transformation (Figure 1). Interestingly, a transcriptomic study in KSHV infection in lymphatic endothelial cells, the cells that are thought to become spindle cells in Kaposi's sarcoma lesions, suggested that there may be a less clear-cut separation between latent and lytic state in terms of viral gene expression in these cell [95]. If that was true *in vivo*, it could explain how lytic proteins, perhaps transiently expressed, could drive oncogenesis by increasing mutations rates.

Oncomodulatory effects of viral infection: the controversial human cytomegalovirus story

With advanced molecular techniques, it is now possible to isolate many viral sequences from tumors, which has generated interest in potential oncomodulatory functions for viruses that are not classically considered tumorigenic. One of the widely debated and highly controversial new ideas is the possibility that the β -herpesvirus human cytomegalovirus (HCMV) may be involved in glioblastoma multiforme. This idea emerged when the isolation of HCMV sequences in glioblastoma [96] and other cancers [97] was reported in 2002.

HCMV also encodes proteins that could be oncogenic, and target known human tumor suppressors, such as RB1 [98,99]. A very recent study showed that the HCMV-encoded chemokine receptor US28 can promote glioma growth and that targeting it with nano-antibodies reduced growth of a HCMV-positive glioma in mouse models [100]. Perhaps the most compelling arguments for HCMV involvement in glioblastoma are patient studies in which treatment with HCMV-reactive autologous T cell ameliorate glioblastoma prognosis [101]. However, HCMV infection is generally cytopathic and not transforming, and therefore HCMV has been proposed to have “oncomodulatory” effects, i.e. the viral infection provides a milieu in which tumor development is facilitated [102–105]. The HCMV-glioblastoma connection remains controversial. In part, this is because it is hard to definitively connect tumorigenesis with such a prevalent virus. Also, not all studies have been able to detect HCMV in glioma samples [106,107], although these results do not rule out a hit-and-run mechanism (see below) given that HCMV can induce genomic instability [108]. It will be hard to establish a causal link for HCMV in tumors until more studies in patients can show a benefit of targeting HCMV and/or HCMV replication.

Hit-and-run carcinogenesis

As mentioned, induction of genomic instability is hallmark of several human cancer viruses. This instability is enabled by the subversion of cell cycle checkpoints, which permits cells with chromosomal aberrations to continue to proliferate. It is possible that once a viral infection has caused a sufficient number of oncogenic cellular mutations for tumor initiation, expression of viral proteins or viral infection is no longer required for tumor maintenance, and, consequently, the virus may be lost during cancer progression. In such scenario, a virus would contribute to carcinogenesis through a “hit-and-run” mechanism, more akin to a chemical carcinogen (Figure 1). As such, hit-and-run carcinogenesis is a variation to the oncomodulation concept as exemplified above.

A well-established example of hit-and-run oncogenesis is the role of β -HPVs in the development of cutaneous squamous cell carcinomas, particularly in long-term immunosuppressed organ transplant patients. Interestingly, viral sequences are detected in precancerous lesions (actinic keratosis) but are absent in the majority of carcinoma cells [6,109]. Since these cancers frequently develop in sun-exposed areas of the skin and β -HPVs interfere with repair of UV-associated DNA lesions and apoptosis, β -HPVs could contribute to carcinogenesis because they enable the accumulation of carcinogenic UV damage [110]. This mechanism has been replicated experimentally in a recent study using a β -HPV38 E6/E7 Cre-loxP-based transgenic mouse model, which develop tumors after UV irradiation even after excision of the viral DNA sequences [111]. Interestingly, loss of β -HPV sequences during carcinogenesis may not be merely accidental, but even necessary for tumor progression. The TGF β and NOTCH signaling pathways, which are repressed by β -HPVs, are tumor suppressive at early stages of epithelial carcinogenesis, but are oncogenic at later stages of malignant progression. Hence the observed loss of β -HPVs in cutaneous squamous cell carcinomas may reflect the necessity for reactivation of TGF β and NOTCH signaling during cancer progression [22]. While α -HPV oncogene expression is generally maintained in the cancers, α -HPVs may contribute to tumorigenesis via a hit-and-run mechanism in Fanconi Anemia patients. These patients harbor mutations in genes that control genomic

stability, and frequently develop oral cancers and squamous cell carcinomas at sites consistent with high-risk HPV infections. Most studies indicate, however, that these cancers are HPV-negative [112]. It is thus conceivable that HPVs may initially trigger carcinogenesis, but that because of the high rate of mutations in Fanconi Anemia patients, the oncogenic pathways initially targeted by E6 and E7 may be rapidly inactivated by mutation. At this point, HPV E6/E7 expression would become dispensable for tumor maintenance. This model is supported by a study in transgenic mice with conditional HPV16 E7 expression. While continued E7 expression was necessary for tumor maintenance in wild-type mice, tumors in mice carrying an Fanconi Anemia mutation continued to grow even after E7 was no longer expressed [113]. Similarly, while HTLV-1 Tax causes genomic instability and is thus key for leukemogenesis, Tax expression is silenced after tumor formation [68,69]. It has been proposed that this is because continued high levels of genomic instability may ultimately become too genotoxic and hamper tumor maintenance [68].

There is a possibility that other human viruses may also contribute to human carcinogenesis through hit-and-run mechanisms. The human BK polyomavirus, for example, has been proposed to be involved in the etiology of some cases of prostate cancer, and it is currently classified by the WHO as a group 2B agent, “possibly carcinogenic to humans” [114]. In animal models, BK virus is clearly transforming, through the activity of its large T and small T antigens [115]. Moreover, BK virus and the BK T antigen protein have been detected in proliferative inflammatory atrophic lesions and prostatic intraepithelial neoplasia, the precursors to prostate cancers [116,117]. However, they are not found consistently in prostate cancer cells, suggesting that BK virus infection might contribute only to early stages of prostate cancer development [118]. Hence, it is possible that hit-and-run carcinogenesis may be more pervasive than is currently appreciated, and that many viruses could act as co-carcinogens, similarly to environmental and chemical agents.

Conclusions

Most human cancers arise by a combination of genetic predisposition, exposure to a variety of environmental factors and “bad luck”. While smoking cessation has the potential to dramatically curb the incidence of a large number of human cancer types, other environmental mutagens such as sun exposure are more difficult to evade. In contrast, virus-associated cancers, even those caused by a hit-and-run type mechanism, can in principle be curbed by prophylactic vaccination prior to exposure. The effectiveness of this approach has been impressively demonstrated in practice by the available prophylactic HBV and HPV vaccines [28,29]. For viral cancers that arise in already infected individuals as a consequence of long-term immunosuppression after organ transplantation or other diseases, another therapeutic approach could be to vaccinate patients with the aim of generating immune responses to non-structural viral proteins. Cancers that are driven by persistent viral infections can also be effectively prevented by treating infected individuals with antivirals. HCV clearance with both the original, less effective ribavirin and interferon-based treatments and the recently introduced HCV protease inhibitors reduces hepatocellular carcinoma incidence, particularly if the virus is cleared prior to the development of cirrhosis [119–121]. The new highly effective anti-HCV drugs in particular afford the opportunity to completely sterilize or at least dramatically decrease the viral burden in most infected

individuals [122]. Lastly, by definition viruses express neoantigens that can be targeted with immune checkpoint inhibitors, potentially in conjunction with therapeutic anti-cancer vaccines [123].

Hence, studies into the viral etiology of cancers will continue to be generate important insights that can be used to combat a large percentage of human cancers.

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Figure 1:

Schematic representation on the interplay of viral (blue) and cellular (red) factors that can contribute to human carcinogenesis. All of the human cancer viruses establish persistent infections, where the virus has managed to reprogram the infected host cell and subvert antiviral defense responses. Viral proteins that serve to reprogram the host cell and blunt antiviral responses often have oncogenic activities. These activities include inhibition of cell death, enhanced proliferation and induction of genomic instability. Inflammatory responses to viral infection produce reactive oxygen species that can drive carcinogenesis by inducing genomic instability and also stimulate proliferation to replaced damaged tissue. Most infections with human oncogenic viruses do not lead to carcinogenesis, and malignant progression generally requires exposure to co-carcinogenic factors. While in many cases virus-associated cancers remain addicted to viral oncoprotein expression, in other cases viruses may only contribute to specific stages of carcinogenesis (“oncomodulatory” viruses) and viral sequences may be lost in the cancer cells (“hit-and-run” carcinogenesis).

Human Cancer Viruses

Table 1:

<i>Virus family</i>	<i>Virus</i>	<i>WHO/IARC Group*</i>	<i>Symptoms, Diseases</i>	<i>Cancer</i>	<i>Viral factors that may promote tumors</i>	<i>Notes</i>
Papillomaviridae (α-genus)	HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	1	Asymptomatic, squamous intraepithelial lesions	Cervical, vaginal, vulvar, penile, anal, oral carcinomas, bladder cancer	E5, E6, E7	>10% of the population actively infected; 80% lifetime infection rate
	HPV68	2A				
	HPV26, 30, 34, 53, 66, 67, 69, 70, 73, 82, 85, 97	2B				
	HPV6, 11	3	Asymptomatic, genital warts			
Papillomaviridae (β- and γ-genus)	HPV5, 8	2B	Asymptomatic, papillomas	Cutaneous squamous cell carcinomas	E6, E7, E2	Confirmed HPV etiology only for tumors in epidermodysplasia verruciformis patients
	Some other β- and γ-genus HPV's	3				
Herpesviridae	EBV	1	Asymptomatic, mononucleosis, autoimmune diseases (?)	Hodgkin's lymphoma, Burkitt's lymphoma, gastric cancer, nasopharyngeal carcinoma	EBNA1, EBNA3s, LMP1, LMP2, EBEB non-coding RNAs, miRNAs	>90% seropositivity
	KSHV	1	Asymptomatic, KSHV inflammatory cytokine syndrome	Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman's disease	LANA, Kaposin, v-cyclin, vFLIP, vGPCR, K1, K15, vIL-6, miRNAs	seropositivity: <10% (US); 20–30% (Mediterranean countries); >50% (sub-Saharan Africa); tumors predominantly in immunocompromised patients
Hepadnaviridae	HBV	1	Asymptomatic, flu-like symptoms, jaundice, cirrhosis	Hepatocellular carcinoma	HBx	350 million infected; 300,000 annual deaths due to liver cancer and 450,000 due to cirrhosis and other causes
Flaviviridae	HCV	1	Asymptomatic, jaundice, cirrhosis	Hepatocellular carcinoma	Core, NS3/4, NS5	143 million infected; 167,000 annual deaths due to liver cancer and 326,000 due to cirrhosis
Retroviridae	HTLV-1	1	Asymptomatic, HTLV myelopathy/tropical spastic paraparesis	Adult T cell leukemia/lymphoma, cutaneous T-cell lymphoma	Tax, HBZ	Prevalence varies: <1% US; >10%, Japan; 10–45% indigenous Australian

<i>Virus family</i>	<i>Virus</i>	<i>WHO/IARC Group</i> [*]	<i>Symptoms, Diseases</i>	<i>Cancer</i>	<i>Viral factors that may promote tumors</i>	<i>Notes</i>
Polymaviridae						peoples; 30–50% amongst IV drug users.
	MCPyV	2A	Asymptomatic	Merkel cell carcinoma	small T, truncated large T	>80% seropositivity
	JCV	2B	Asymptomatic, Progressive Multifocal Leukoencephalopathy	?	T antigens?	
	BKV	2B	Asymptomatic, nephropathy	Prostate cancer?		

^{*} Group 1: Carcinogenic to humans; Group 2A: Probably carcinogenic to humans; Group 2B: Possibly carcinogenic to humans; Group 3: Not classifiable as to its carcinogenicity to humans