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Regulating cellular plasticity to persist: a way for tumor viruses to triumph

Vural Yilmaz and Katerina Strati

Address
University of Cyprus, Department of Biological Sciences, 1 University Avenue, 2109, Nicosia, Cyprus

Corresponding author: Strati, Katerina (strati.katerina@ucy.ac.cy)

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Introduction

Viruses can cause cancer either by direct (e.g. expression of viral oncogenes) or indirect (e.g. immunomodulation) means. A pre-requisite to carcinogenesis is long-term infection of the natural niche, indicating an important link between the ability to establish persistent infections and eventual tumorigenesis. Persistently infected cells are thought to serve as the cells-of-origin in infection-associated cancers. As is the case with non-infectious cancers, it has been proposed that infected tissue stem cells may give rise to the cancer-initiating cells. Emerging evidence points to an alternative possibility that infected committed cells may acquire stem-like characteristics during infection, giving rise to tumor-initiating cells.

Here in this study, we summarize similarities and differences of the mechanisms used by human tumor viruses to evade the host immune system by promoting persistent infection and tumor formation. Moreover, we explore the possible benefit of infecting stem cells or reprogramming differentiated cells to more stem-like phenotypes by the human tumor viruses to aid the viral lifecycle and/or disease progression.

Human tumor viruses

Over 20 different types of cancers have been linked or possibly linked to infections caused by viruses [1]. Epstein–Barr virus (EBV) was the first virus identified to cause cancer in humans which was linked to Burkitt lymphoma. Since then, in addition to EBV, six other viruses or families of viruses are known to cause tumorigenesis in humans (Table 1). These seven human tumor viruses establish different interactions with their particular host cells based on their structural and functional characteristics [2]. Even though the number of these human tumor viruses is small, interestingly they span the entire range of virology. Also, almost all of these viruses have close relatives that do not cause tumorigenesis [3]. This raises questions as to why and how these small group of human viruses can initiate tumorigenesis.

Persistent infections by the human tumor viruses, evading antiviral responses

The host's immune system is a key factor in determining whether cancer is the outcome of a virus infection. A common feature of the human tumor viruses is their tendency to persist in chronic infections since virus-associated cancers arise years or decades after the initial infection. Long-term infection requires effective evasion of innate and adaptive immune responses of the host for extended periods of time.

The mechanism to remain latent in the host depends on the type of the tumor virus (Figure 1). Oncogenic retroviruses such as HTLV-1 are reversely transcribed into a double-stranded DNA, with a further integration into the chromosomal DNA [4]. Another virus with an RNA genome, HCV, in contrast to HTLV-1, lacks the capacity to integrate into the host genome. As a consequence, HCV exerts its carcinogenic influence via chronic inflammation [5]. DNA tumor viruses such as EBV, HPV, HBV, and KSHV usually persist by either integrating in the host genome or by remaining episomally. However, genome integration of the DNA tumor viruses is not necessarily associated with persistent infection since fragmentation and integration of viral DNA into the nascent tumor cell can eliminate their ability to replicate as virions, a state that some have termed 'pseudo-latency' [3]. In this case, a number of sequences are lost during integration and no virus can be produced even though the viral sequences are persistently expressed in the cell. Furthermore, while viral latency is a well-accepted and described lifestyle for some of the DNA tumor viruses such as EBV and KSHV, it still remains a somewhat controversial matter for others such as HPV.

Keeping a close check on viral transcript expression is also important for human tumor viruses to sustain persistent infections. For example, MCV LT domain binds lysosomal cluster protein, hVamp6, which reduces MCV replication in 293 T cells [6]. In addition, an miRNA encoded by MCV can downregulate its early gene transcription [7]. Latent viral protein expression of herpesviruses, for example, is limited to a few crucial, non-structural viral products that include oncogenic

Table 1

Human tumor viruses

Virus	Genome	Cancer	Contributing factors to persistent infections
Epstein–Barr virus (EBV)	Double-stranded DNA herpesvirus	Most Burkitt's lymphoma and nasopharyngeal carcinoma, most lymphoproliferative disorders, some Hodgkin's disease, some non-Hodgkin's lymphoma and some gastrointestinal lymphoma	Generates an episome that contains circular EBV genome, which remains in a latent form and resides quiescently in resting memory B-cells
Human papillomaviruses (HPV)	Double-stranded DNA papillomavirus	Most cervical and penile cancers, some other anogenital and head and neck cancers	Maintains viral genomes as extrachromosomal episomes that tether to host DNA and continuously replicates at low levels in the basal epithelium
Hepatitis B virus (HBV)	Single-stranded and double stranded DNA hepadnavirus	Some hepatocellular carcinoma	Suppresses immune system and forms covalently closed circular DNA (cccDNA) that is sequestered inside the nucleus
Hepatitis C virus (HCV)	Positive-strand, single-stranded RNA, flavivirus	Some hepatocellular carcinoma and some lymphomas	Establishes chronic inflammation in the liver and replicates in the cytoplasm without integration into the host genome
Merkel cell polyomavirus (MCV)	Double-stranded DNA polyomavirus	Most Merkel cell carcinoma	Sustains continuous cellular turnover of its own replication proteins and persists as a nonreplicating silent infection
Kaposi's sarcoma herpesvirus (KSHV)	Double-stranded DNA herpesvirus	Kaposi's sarcoma, primary effusion lymphoma and some multicentric Castleman's disease	Viral genome remains episomally and is mediated by the viral protein called Latency-associated nuclear antigen (LANA)
Human T-lymphotropic virus-I (HTLV-I)	Positive-strand, single-stranded RNA, retrovirus	Adult T cell leukemia	Reversely transcribed into a double-stranded DNA with a further integration into the chromosomal DNA. Stimulates cell growth via viral proteins such p12, p13, and p30.

proteins and microRNAs that suppress viral propagation [8]. Additionally, papillomavirus E6 and E7 transcription was shown to be negatively regulated by the viral protein E2 [9].

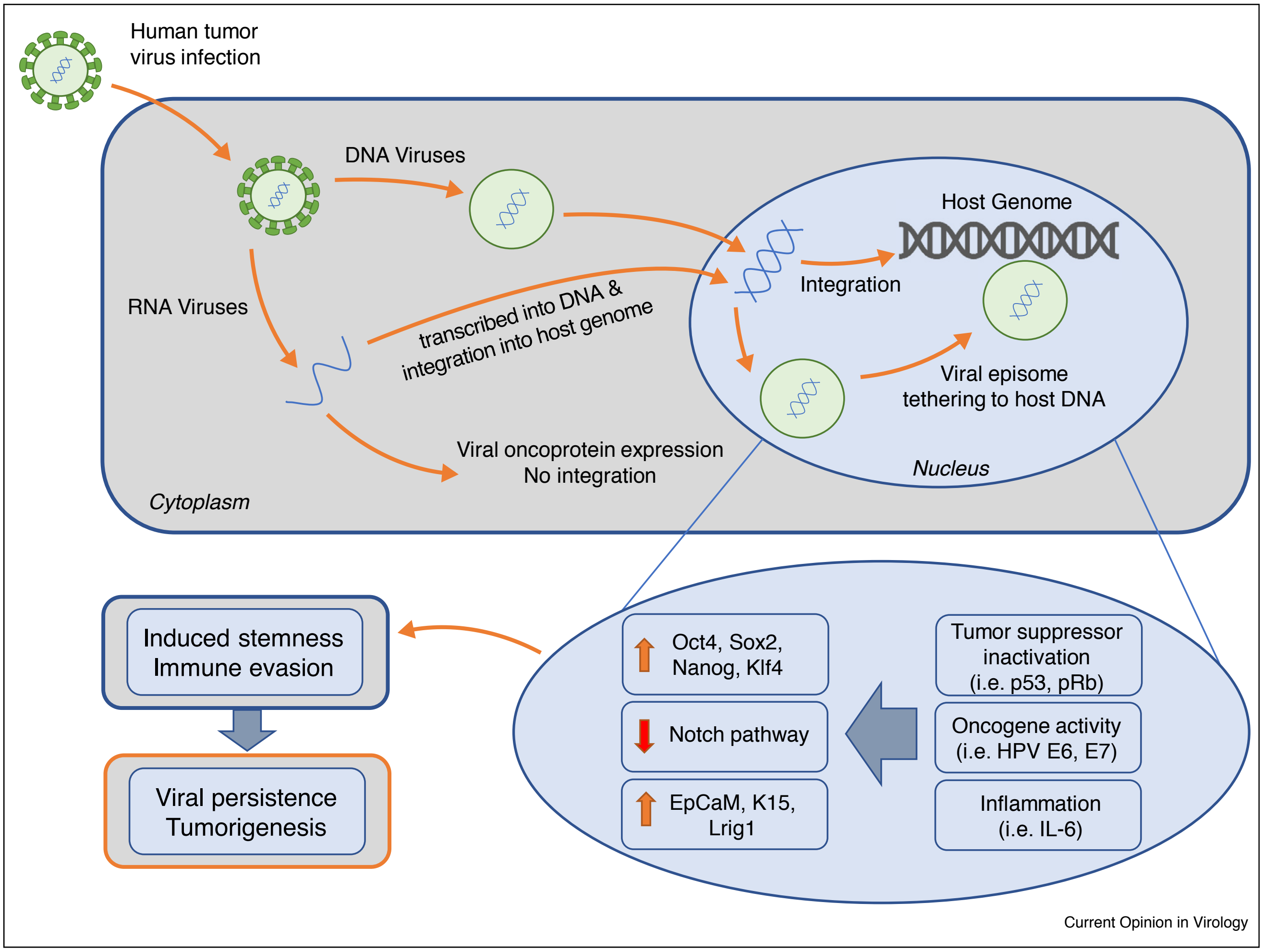
Targeting tumor suppression as a mechanism to establish persistent infection

Innate immune signaling shares many similarities to tumor suppressor signaling, as both processes initiate cell cycle arrest and prime apoptotic pathways. Key effector proteins such as the p21 [10] and p53 [11] are shared by both tumor suppressor and innate immune surveillance signaling networks. This suggests that targeting of tumor suppressor pathways by viruses may actually represent an immune evasion response that disables antiviral pathways but inadvertently places the infected cell at risk for cancerous transformation (also known as the anti-antivirus hypothesis) [12].

The relationship between tumor suppression and cellular antiviral activity was described previously by showing that knock out of Trp53 (encoding p53) causes immune deficiency to especially virus infection, and that virus induced inflammatory cytokines prime cellular pro-apoptotic signaling pathways [11]. Other cellular pathways with roles traditionally associated to preventing tumorigenesis might also play a part in immunity to viral infection [13]. Cellular sensors for DNA and RNA ends are generally studied as triggers for the repair of somatic mutations but they also have a role in sensing viral nucleic acids [14,15]. DNA damage responses are activated during viral replication that can lead to cell cycle arrest and inflammatory signaling [16]. This means that disarming the antiviral targeting of tumor suppressor signaling by human tumor viruses may be required to allow viral replication to proceed but also contributes to prolonged persistence of viral infection and has a secondary biological consequence in generating a cancer-permissive environment. This scenario is in line with the notion that the carcinogenesis by tumor viruses is likely a biological accident since the viruses that are found in the tumors are not replicative or infectious [17].

Other targets which perform double duty in innate immunity and tumor suppressor signaling are the interferon regulatory factors (IRFs), the early response transcription factors that regulate interferon transcriptional responses [18,19]. KSHV encodes several factors that have well-defined innate immunomodulatory roles in inhibiting interferon signaling and initiating cell transformation. For example, vIRF1 [20], IRF2 [21], interleukin-6 (vIL-6) [22], FLICE inhibitory protein (vFLIP) [23], ORF K1 protein [24], latent nuclear antigen 1 (LANA1) [25] and LANA2 [26]. For EBV, latent small non-coding EBV RNAs (EBERs) are known to target RNA-dependent protein kinase (PKR) immune signaling that might have a role in EBV-induced tumorigenesis [27]. Together, these studies point to a common mechanism of tumor viruses to form persistent infections by targeting tumor suppression as an immune evasion strategy.

Figure 1



Human tumor viruses can regulate cellular plasticity to induce stemness, evade host immune system and establish persistent infections. Human tumor viruses have different mechanism to establish latency: DNA tumor viruses either integrate into the host genome or remain episomally, tethering to host chromosome while RNA tumor viruses are either transcribed into DNA with further integration into host genome or remain in cytoplasm with no integration. To establish persistent infections, human tumor viruses are known to regulate host tumor suppression mechanisms such as p53 and pRb and target immune pathways. More recent evidence suggests that stemness-associated transcription factors and mediators (i.e. Oct4, Sox2, Nanog, and Klf4) are also deregulated. This manipulation of cellular plasticity contributes to induced stemness and immune evasion that leads to tumorigenesis and may also contribute to viral persistency.

Harnessing stemness contributes to ensuing carcinogenesis

Stem cells are of great interest when considering persistent infections and the consequent carcinogenesis of human tumor viruses. The relative scarcity of such cells in tissues makes their exclusive targeting a rather unlikely scenario. However, given the high longevity and the cellular plasticity of the stem cells, one can imagine significant advantages upon infection of a cell with such characteristics, conceivably as a result of preferential infection or differential outcomes compared to other target cells.

Differential outcomes upon infection of stem cells have already been reported for non-tumorigenic viruses. For example, Human Cytomegalovirus (HCMV) appears to primarily target stem cells and progenitor cells in the subventricular zone (SVZ) of the brain [28,29], and the infection of HCMV of stem cell population might be a way for the virus to successfully establish lifelong latency in the host [30]. More recently, it was also shown that Zika virus (ZIKV) consistently infects human cortical neural progenitors in the brain in particular with significant pathological impact [31•] and that infecting these progenitors causes a differential outcome of the disease progression compared to infecting other cells, by restricting their growth [32].

In regards to this, a popular hypothesis has been that long-term preservation of viral genome can take place within infected tissue stem cells [33]. This is especially relevant to asymptomatic persistent infections which can be the source of tumorigenesis caused by human tumor viruses. For example, stem cells in cutaneous epithelia are typically slow-cycling and can perform asymmetric division, dependent on the cellular niche, generating one stem and one transiently amplifying progenitor cell [34]. One might argue that this could be the perfect host cell for human tumor viruses to stay under the radar of immune system and maintain its replication asymptomatically; eventually causing tumorigenesis.

Another possibly advantageous characteristic of the stem cells may be intrinsic mechanisms that grant them an at least partial immune privilege. Even though there are still outstanding questions about the immunogenicity of the stem cells, recently quiescent stem cells were shown to be able to escape the immune surveillance [35•]. Furthermore, it was found that this was a result of systematic downregulation of the antigen presentation machinery [35•]. In contrast, there have been several other studies with embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs) where ESCs were found to be only transiently immune privileged but where they can still be eliminated by an adaptive immune response in certain circumstances [36]. MSCs in contrast appeared to be immune modulatory rather than immune privileged [37,38]. In addition, ESCs have long been known to exhibit a specific ability to potently suppress the expression of both exogenous and endogenous retroviral sequences in order to protect the integrity of the host germ line [39,40]. Nevertheless, these studies indicate a somewhat differential treatment for stem cells by the host's immune system. For tumor viruses, this partial immune privilege of stem cells would be an enormous benefit to maintain their presence and proliferate without the possibility of detection and elimination.

In the case of HPV, it has been already proposed that the virus may be more successfully maintained [33,34], and indeed infected cells are more likely to proceed to tumorigenesis when the initially infected cell is a tissue stem cell [41]. There is however also evidence which supports an alternative scenario that during HPV infection it is possible that reprogramming events can contribute to the emergence of stem-cell like cells. For example, it was previously shown that the increased stem cell mobilization seen in transgenic animals is also concurrent with the expression of stem cell markers such as Keratin15 (K15) outside the typical stem cell niche [42]. The expression of early genes from the cutaneous HPV8 has also been shown to lead to an expansion of stem cell markers, specifically leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1) [43].

It is now thought that increased cellular plasticity (the ability of cells to assume characteristics of other cells) may have functional significance in the pathogen lifecycle and disease. Indeed, it was suggested before that even partial reprogramming can erase cellular markers of aging in both mouse and human cells [44]. This 'rejuvenation' can be advantageous to tumor viruses. Reprogramming is an epigenetic process which gradually shifts the transcriptional program of a differentiated cell to that of a pluripotent one. The upregulation of genes related to stem cells through reprogramming may also be a way, in which the virus contributes to the formation and maintenance of the so called 'cancer stem cell' (CSC) populations. A recent study shows that this induced stemness can provide an escape from immune surveillance by enabling a slow-cycling state which downregulates cell-surface-innate immune sensors [45••]. The expression of stem cell related markers is now increasingly reported in HPV-related cancers [46•,47]. Recently E6 has been shown to be upregulated in cancer stem cell-like cells isolated from primary cervical tumor cell lines [48••]. These cells were also shown to express Oct4, Sox2, Nanog, and Lrig1 and were dependent on E6-mediated expression of Hes1 for continued self-renewal.

Naturally, inflammation induced by the viral infection also has a relevance here. In fact, the link between the inflammation and stem cells has direct implications on carcinogenesis [49•]. It was shown before that stem cell recruitment and differentiation are directly linked to increased inflammation. For example, CD34+ progenitor cells are recruited to sites with increased inflammation, through the regulation of adhesion and chemokine receptors such as CXCL12 and CD44 [50]. In addition, inflammatory mediators seem to have a crucial role in reprogramming events and in promoting the expression of stemness-related genes. This induction of stemness is likely to be linked to the generation and evolution of the cancer stem cells [51]. For example, upregulation of OCT4 due to inflammation has been shown to contribute to tumor cell migration and resistance to cancer therapeutics [52••,53]. Consequently, it also seems beneficial for human tumor viruses to manipulate inflammation to aid establishing persistency.

Several other human tumor viruses may follow a similar strategy of either preferentially infecting stem cells or inducing stemness in the already differentiated infected cells that may provide latency and a shield for the immune system. For example, KSHV and EBV infect primarily resting mature B cells. However, these cells are short-lived and non-proliferating, which points to the possibility that herpesviruses may also infect a progenitor, stem cell-like population of B cells, to ensure continuous viral genome propagation and viral latency maintenance. Indeed, KSHV has been detected in immature hematopoietic cells in the bone marrow of transplant recipients [54,55] and in hematopoietic progenitor cells in Kaposi's sarcoma patients [56,57]. In an interesting study, Kong *et al.* investigated the role of EBV LMP2A protein in CSC modulation in nasopharyngeal carcinoma (NPC) cells, and showed that expression of this protein induced cell invasion and epithelial-mesenchymal transformation (EMT) [58]. Overexpression of LMP2A was found to enrich stem-like cells within the NPC tumor cell population, and increased the number of cells that were capable of re-establishing tumors in nude mice [58]. These results were then confirmed in NPC patient biopsies, further suggesting that a possible mechanism of tumorigenesis in EBV-infected tissues is the modulation of the tissue stem cell compartment and the induction of tumor-initiating CSCs. This notion is also highlighted by a more recent study [59], which demonstrated upregulation of multiple stem cell markers in an EBV-positive NPC cell line with increased tumorigenic potential and high resistance to chemotherapy.

Furthermore, recently it was shown that HBV might induce initiation of hepatocellular carcinomas (HCC) by activating cellular factors that promote stemness [60]. HBV encoded X antigen (HBVx), important in the viral life cycle as well as carcinogenesis, was shown to activate stemness associated factors Oct-4, Nanog, Klf4, beta catenin, and EpCAM *in vitro*. These stemness associated markers were also observed in the majority of HBV-associated HCCs [60]. HCV has also been implicated in induction of stemness. Machida *et al.* isolated tumor initiating stem-like cells from transgenic mice expressing HCV core, as well as from patients with HCC, and showed that the TLR4-Nanog pathway was upregulated in these cells and was necessary for their tumorigenic properties [61,62]. Nanog, a stem/progenitor cell marker was further shown to be upregulated through activation of the TLR4 pathway by NS5A, a non-structural protein encoded by HCV [62].

Conclusions

Despite their diversity, human tumor viruses show similarities in lifestyle strategies not only in their evasion of the immune system but also in their quest toward 'stemness'. Such strategies inevitably contribute to eventual carcinogenesis but the likely objective is persistence. Studies reviewed here show that these viruses target pathways that are important in a number of major cellular processes including cell proliferation, cell division, apoptosis, cell differentiation and antiviral defense mechanisms. It is now apparent that many tumor-suppressing factors of the cells are targeted by human tumor viruses not only to manipulate the cell cycle but also to suppress some of the antiviral defense system of the cells. In this way, the tumor viruses manage to efficiently sustain their persistency; eventually resulting in tumorigenesis. Finally, accumulating evidence suggests that human tumor viruses may also benefit from infecting tissue stem cells or promoting cellular stemness (including aberrant forms of cellular plasticity). This is a direct outcome of the regulation of pathways that are traditionally associated with self-renewal and lineage-commitment. It is plausible that such an endeavor positively affects the viral life cycle, especially in terms of establishing a successful persistent infection (Figure 1). Even though additional studies are necessary to further investigate the regulation of stemness by human tumor viruses and its possible consequences on the onset of tumorigenesis, our increasing understanding of these processes hold the promise of offering new and efficient clinical interventions to cancers caused by human tumor viruses.

Conflict of interest statement

Nothing declared.

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